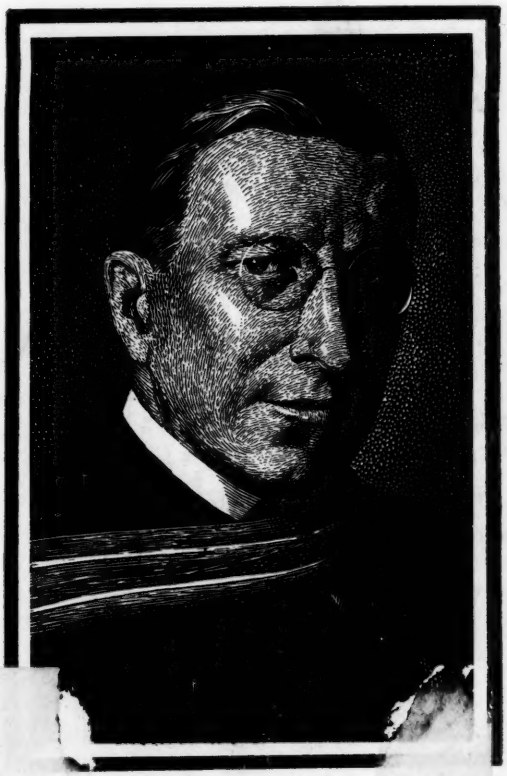
DIABETES

The Journal of the American Diabetes Association



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SHORT TYPE

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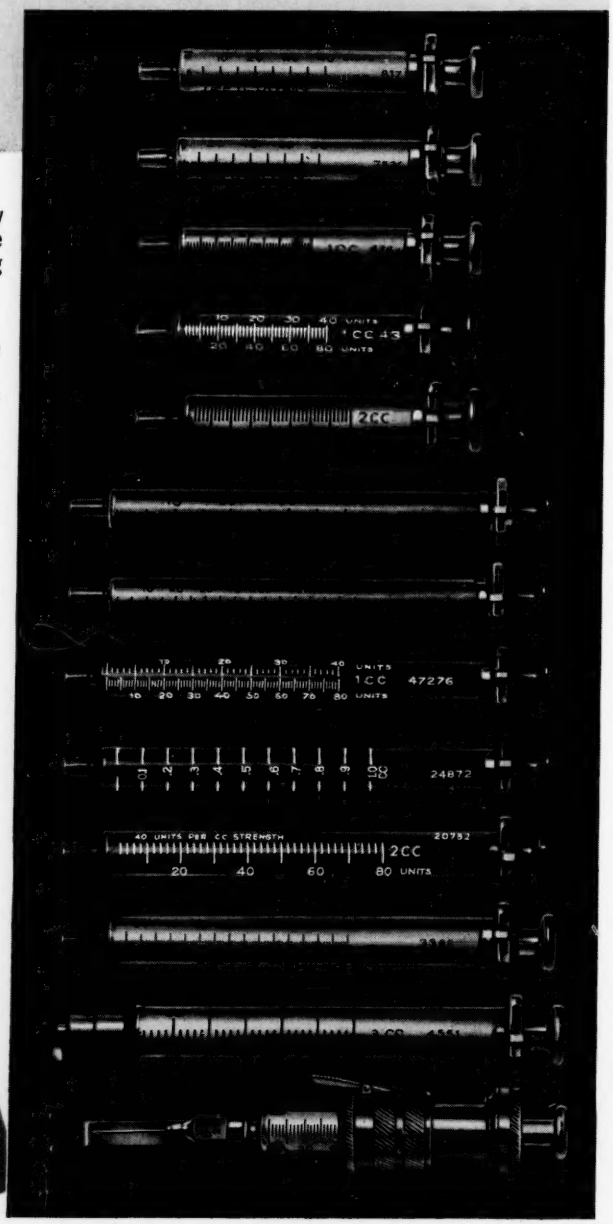

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Salute to

DIABETES

Elliott P. Joslin, M.D.

BOSTON
HONORARY PRESIDENT
AMERICAN DIABETES ASSOCIATION

When we were young, we were told: "Hitch your wagon to a star." The American Diabetes Association is still young, and I think it is hitching its wagon to a very important star with its new Journal, DIABETES.

Two previous publications of the Association, its *Proceedings,* appearing annually, and *Diabetes Abstracts,* heretofore a quarterly, are now combined in the new Journal. All who have known the *Abstracts* have recognized its worth, which has increased with every issue since it first appeared in 1941. Whenever one seeks information from it on any topic relating to diabetes, one finds no essential work done anywhere in the world has been omitted.

The significance of the *Proceedings* of the American Diabetes Association has grown continually over the years as well. The scientific articles read at the Annual Meetings and reprinted in this series of volumes have represented increasingly authoritative presentations of the subjects calling most urgently for discussion and solution in our special field.

Heretofore these two publications have been limited in distribution primarily to the membership of the Association, almost wholly confined to the United States and Canada. The new Journal, however, is available to

interested readers everywhere and will serve as a splendid medium for the dissemination of the latest and most important researches on diabetes throughout the whole civilized world.

This is of paramount importance. Diabetes is a universal disease. It knows no political boundaries. What happens anywhere in the world to improve the condition of the diabetic is important to diabetics everywhere else. One of the major reasons for the founding of our Association was that it should aid in the spread of knowledge about the disease and that reason is now finding its fully effective expression in the publication of DIABETES.

Science has no boundaries, as DIABETES should emphasize both through its contributors and through its subscription rolls. We all have the same purpose: to discover methods of prevention or cure of diabetes. Is there anyone anywhere who would withhold the news of such discoveries from the world? I doubt it! No one would care particularly in what country such a discovery was made, but everyone would care deeply if that country tried to restrict the information. DIABETES will be devoted to spreading worldwide every bit of useful information about the detection, diagnosis, management, prevention and cure of the disease, with no restrictions, no withholding, no censorship.

The diffusion of knowledge about diabetes resulting from the publication of our new Journal should stimulate research. Research material and ideas are by no means limited to great medical centers or large laboratories. Thomas Willis found them in Oxford, England; the United States Public Health Service and local physicians discovered them in Oxford, Massachusetts. There are 21 Oxfords in these 48 states—and many thousands of towns like them. Toronto and Strasbourg are not the only cities where research opportunities are available, either. There are hundreds of others, all equally suitable for great discoveries in the field of diabetes.

The ultimate objective of diabetes therapy is the care of the worldwide diabetic family. This involves the treatment of its members, the detection of those whose disease is still hidden early enough to make simplified control possible, and the prophylaxis of all those who have not yet developed the disease. I conceive that our new DIABETES can become a powerful weapon in bringing about this desired goal.

How enthusiastically Sir William Osler would have greeted the appearance of DIABETES! I am sure that, in expressing his hearty approbation, he would have extended to physicians the same message he gave to Toronto medical students on the Master Word in Medicine—Work. For work, in medical research and the practice of medicine as in every other branch of human activity, is the secret of success, if it is intelligently and selflessly planned and carried out. Sometimes I feel sorry that Dr. Osler never quoted a saying which is commonly attributed to Isidore, the Archbishop of Seville in the early part of the 7th Century. He would have enjoyed repeating it, just as I do:

Disce ut semper victurus, vive ut cras moriturus. Learn as if you would live forever, live as if you would die tomorrow.

In diabetes research, in diabetes therapy, in every aspect of our attack on this disease, including the publication of our own Journal, DIABETES, let us follow in Bishop Isidore's footsteps. They will take us far, if we stay with them.

THE BANTING LECTURE, 1951

The Endocrine Control of the Blood Sugar

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STERLING PROFESSOR OF PHYSIOLOGICAL CHEMISTRY, YALE UNIVERSITY, NEW HAVEN

The study of diabetes mellitus in man and of experimental diabetes produced by various means in animals has already furnished a wealth of information on the nature of those chemical transformations in living cells that we term metabolism, and upon which all bodily function depends. Let me recall to you a few of these landmarks of our knowledge that have been established by observation and experiment on the diabetic organism. First, the recognition by physicians in several countries that the sweetness of diabetic urine was due to the presence of a sugar, later identified as glucose. Then the detection of beta-hydroxybutyric acid and acetoacetic acid as constituents of diabetic urine, which led in time to an appreciation of the nature of acidosis; the relationship between protein catabolism and glucose formation; and, of course, the recognition that there was an internal secretion of the pancreas provided by the islets of Langerhans.

The intensive search for this agent, now known as insulin, culminated with the announcement of Banting and Best in 1921 that they had succeeded in preparing pancreatic extracts that not only corrected the disordered metabolism of the depancreatized dog, but also brought hope for life to millions of diabetics throughout the world. The story of Banting's genius as an experimental scientist has been told by others far more competent than I to do it justice. I should like, however, to add my small tribute since you have honored me by inviting me to give the lecture that now bears his name.

It seems to me that Banting's greatness lay in his ability to formulate concepts that were capable of experimental test. He was not deterred by the repeated failure of his predecessors or contemporaries to isolate the elusive pancreatic agent. He seized upon an old observation that duct ligation, while causing atrophy of the acinar tissue, does not—at least for a time—destroy

the islet tissue. It little matters now that this is an unnecessary preliminary for the isolation of insulin. What is important is that he had this vision and it did lead to the demonstration of the existence of the hormone. I am sure Banting would agree that he was aided by two good strokes of fortune. The first of these was the selection of a young medical student named Best as his assistant. The second was that a few years previously a method for the rapid and accurate determination of glucose in small quantities of blood had been developed. Yet this is the pattern of most great discoveries. In this case Banting, Best and the blood glucose method came together at the appointed time and place and the result was the discovery of insulin.

The problem of the nature and mechanism of the factors that regulate carbohydrate metabolism and consequently the blood glucose level can be rather simply presented. A normal man or woman can ingest several hundred grams of carbohydrate a day without the level of glucose in the blood rising much above 160 mg. per cent. On the other hand, the same individual can subsist on a diet practically free of any preformed carbohydrate or may even fast for many days without the blood glucose falling much below 70. Thus, with a dietary intake of carbohydrate ranging all the way from zero to 400-500 Gm. a day, the corresponding variation in the blood glucose level is only 90 mg. per cent. This in itself indicates that the factors regulating carbohydrate metabolism are unusually precise in their operation and are of such a nature that at no time does the level of glucose in the blood fall below a certain minimal value, or rise to excessive heights. Although I have chosen to speak upon the influence of certain endocrine organs on carbohydrate metabolism, it must be remembered that their hormones are not the only factors that are responsible for the regulation of the metabolism of this foodstuff. The various organs of the body play varying but essential roles in the maintenance of a normal metabolism. Indeed, it must be remembered that the hormones do not initiate metabolic transformations, but merely influence their rate.

PHYSIOLOGICAL MECHANISMS CONTROLLING THE BLOOD GLUCOSE LEVEL

I have just mentioned that the endocrine system is one of several mechanisms that act to maintain the blood glucose between the levels that we regard as normal. Before proceeding to a discussion of the effect of their hormones, it would be well to recall the part played by the various organs of the body. It must also be remembered that the level of glucose or any other metabolite at any particular moment is a resultant of the rates of those processes which either add or remove it from the blood.

Glucose is made available to the tissues either by the carbohydrates or proteins of the diet or in the fasting state from the catabolism of the tissue proteins themselves, while it is largely utilized by the skeletal muscles and, to a more limited extent, by the other organs of the body.

The processes of digestion leave in the intestinal canal, for absorption into the body, a mixture of the three monosaccharides—glucose, fructose and galactose —together with those amino acids which by later transformations can serve as a source of blood glucose. Since fructose and galactose are readily transformed into glucose after absorption, the main problem of carbohydrate metabolism is largely that of the metabolism of glucose.

The rate of absorption of glucose from the intestine, while it is to a large extent independent of the concentration, is effected by specific metabolic processes in the intestinal wall which are of such a kind that the quantity of glucose transferred across the mucosa is within the assimilatory capacity of the tissues. This may be regarded as the first in a series of processes that prevent the blood glucose rising to excessively high levels during periods of high carbohydrate ingestion. The rate of glucose absorption is affected by endocrine factors, for it has been shown to be decreased in hypophysectomized animals—a defect that is corrected by the injection of thyroxin.[1] Furthermore, thyroidectomy or hypothyroidism in man is also associated with decreased absorption while either experimental or clinical hyperthyroidism increases the rate to a marked degree.[2] In other words, the rate of intestinal absorption is adjusted to the metabolic rate of the tissues. It may also be remarked that changes in the composition of the diet alter the rate of intestinal absorption since it is most rapid on a high carbohydrate and slowest on one low in this foodstuff. Since it is also known that changes in the composition of the diet alter the relative activity of those members of the endocrine system concerned with the control of metabolism, we may gain from a study of the intestinal absorption of glucose some insight into the nature of the regulation of carbohydrate metabolism.

The next organ in the body that participates in the supply of glucose to the tissues, and hence influences the blood glucose level, is the liver. This organ not

only retains a considerable portion of the absorbed glucose as glycogen for future needs, but of even greater importance is its capacity to form glycogen from non-carbohydrate substances (gluconeogenesis) and hence add glucose to the blood at times when either no food is ingested or when the diet is low in preformed carbohydrate. Here again the rate of glycogen formation, as well as the rate of its release to the circulation, is significantly affected by endocrine factors. For instance, it is well known that epinephrine and probably a hyperglycemic factor from the pancreas accelerate glycogenolysis.[3] Insulin influences the rate of glycogen formation from glucose while—as will be shown later—the rate of carbohydrate formation from the products of protein catabolism (gluconeogenesis) is under the control of the adrenal cortical hormones.

The kidney tubules also play an important, if not always appreciated, role in the regulation of blood glucose. It is well known that all the glucose of the plasma is filtered into the glomerular fluid from where, under normal conditions, it is completely reabsorbed into the circulation by the specific activity of the renal tubules. The metabolic processes involved in this transfer of glucose across the tubular cells are probably very similar to those operating to transfer glucose across the intestinal mucosa. At any rate there is a maximum limit to their capacity to remove glucose from the glomerular fluid which may be exceeded when too much glucose is presented to them. This maximal absorptive capacity is influenced not only by continued exposure to high glucose levels in the glomerular fluid, frequently expressed by the so-called raised renal threshold in diabetes, but apparently by the activity of the endocrine system. Thus it has been reported that the maximum renal absorptive capacity for glucose is increased in hyperthyroidism, while certain adrenal steroids are said to cause a decrease. The classical example of the effects of interference with tubular reabsorptive capacity is that of phloridzin poisoning. Here the inhibition of reabsorption produced by the drug not only lowers the blood glucose, but forces the organism to make good the urinary loss of glucose by an enhancement of gluconeogenesis. The kidney also shares with the liver the ability to form glucose from carbohydrate sources. How important a contribution this may be to the maintenance of blood glucose is not exactly known, but recent studies indicate that under some circumstances it may be in amounts of considerable significance.

We may conclude at this point that the rate of entry of glucose into the circulation is regulated by the activity of three organs. These are the intestine, the liver, and the cells of the proximal renal tubules. Among these the liver is the most important since it not only releases its preformed stores of glycogen, but manufactures glucose for the needs of the body from smaller molecules derived either from the intermediary metabolism of protein or carbohydrate.

UTILIZATION OF GLUCOSE BY THE TISSUES

Glucose, whether derived from dietary sources or furnished to the body by the activity of the liver, is utilized in the tissues by three pathways of metabolism.

The first of these is by transformation to glycogen either in the liver or muscles. While the subsequent pathway of degradation of glycogen is different in these tissues, the muscle glycogen only indirectly serving as a source of blood glucose, the synthetic mechanism appears to be identical. The most important step in carbohydrate utilization is the formation of glucose 6-phosphate from glucose. This reaction, which is catalyzed by the enzyme hexokinase, has been suggested by the Coris and their colleagues[4] as the point upon which both insulin and an unidentified anterior pituitary hormone exert their effects. Their experiments suggest that the pituitary factor inhibits this enzyme—an effect that would reduce glucose utilization in any form and lead to the accumulation of it in the blood. Insulin, on the other hand, is said to remove the inhibition imposed by this pituitary hormone and would, in consequence, increase glucose utilization.

The second method of utilization of glucose is by oxidation to carbon dioxide and water. This is brought about by a preliminary series of transformations by which either a three-carbon derivative, pyruvic acid, or an unknown two-carbon compound is formed. Either, or both of these, is then oxidized in a stepwise manner by the action of a series of enzymes and catalysts over a pathway that is known as the tricarboxylic acid cycle. This cycle is also believed to be the final common oxidative pathway for the intermediary metabolites derived from the catabolism of fatty acids and proteins.

The last pathway of carbohydrate utilization, and one about which least is known, is the formation of fatty acids. This transformation, as the work of Stetten and Boxer[5] has shown, is quantitatively the most important. The fatty acids formed in this manner may be stored to an almost unlimited extent in the fat depots or may be more immediately utilized for the needs of the organism.

These, then, are the main pathways of glucose utilization and consequently variations in the rate of these

processes will determine to a large extent not only the level but the direction of change of the blood glucose. Indeed, the regulation of the blood glucose level by the hormones is affected by influencing these metabolic transformations in the various tissues of the body.

THE EFFECT OF INSULIN ON THE UTILIZATION OF CARBOHYDRATE

The importance of insulin in preventing an excessive increase in blood glucose is due to its capacity to accelerate the rate of utilization of carbohydrate in the tissues. It is, in fact, the only hormone that does this since all others either do not affect the blood glucose level or else increase it.

The work of recent years has shown that insulin has an effect upon all three main pathways of carbohydrate utilization. Thus it increases glycogen formation from glucose both in the muscles and liver. In the latter this effect may be masked if the insulin is contaminated with the hyperglycemic factor from the pancreas. The possible participation of insulin in the hexokinase reaction has already been mentioned.

Insulin has also been shown to participate in those processes by which glucose is converted to fatty acids. In its absence from the body, as Stetten and Boxer[5] and others[6, 7] have shown, the amount of dietary glucose transformed into fat is reduced to some 10 per cent of the normal rate.

The participation of insulin in the cyclic changes that result in the complete oxidation of glucose intermediaries to carbon dioxide and water has also been suggested. At the present time, however, unequivocal evidence that insulin directly catalyzes any one of the reactions of the tricarboxylic acid cycle is not available.

The participation of insulin in the formation of fatty acids allows some deductions to be made on the nature of the well-known relationship between obesity and the occurrence of diabetes in man. In an individual who is maintaining a constant body weight, the energy represented by the food intake is balanced by that expended in the bodily activities. It may be assumed that the transformations undergone by carbohydrates or their metabolites require that the pancreas furnish a certain quantity of insulin a day (x) to accomplish them.

On the other hand, an individual who habitually ingests carbohydrates and other foodstuffs in excess of the needs of the daily energy requirements deposits fatty acids in the depot areas of the body. The fatty acids formed from carbohydrates, but not used, nevertheless require a certain amount of insulin (y) over and above that needed by those who maintain a constant body weight, and this insulin to all intents and purposes is wasted. In other words, the continual and unnecessary addition of fat to the body stores may be regarded in its effect on the pancreas as equivalent to a partial pancreatectomy. Furthermore, when it is remembered that this addition of unnecessary quantities of fat goes on for months and years, it is perhaps not surprising that ultimately the islet tissue becomes unequal to the demands placed upon it. The insulin deficiency will be insidious in its development and at least for a time may be corrected if measures are undertaken to restrict the food intake to a point where the excessive fat in the body is restrained. That it can occur has been shown by Newburgh whose success in the restoration of normal carbohydrate tolerance in a certain proportion of obese diabetics is known to all. It is also reflected by the recognition that an important part in the treatment of obese diabetics is to return them to normal body weight.

On the other hand, it is equally apparent that in certain other obese diabetics, the functional impairment of the islet cells may have proceeded to the point where merely restoring the body weight to within normal limits still leaves them with a deficient insulin production for their needs. In such cases only the administration of insulin can restore their requirement for this hormone.

Lawrence[8] has named the diabetes associated with obesity "lipoplethoric diabetes." His explanation for the high incidence of diabetes in the obese middle-aged man or woman is somewhat different from that given above. He suggests the hyperglycemia and glycosuria are a reflection of the deficient capacity of the overloaded fat cells to form more fat from carbohydrate. It may well be that the point of fracture in the metabolism of these individuals is in the peripheral tissues, but it seems equally possible that the fragile cells of the islets of Langerhans are the first to yield.

Some work carried out in my laboratory on the effects of experimental obesity on carbohydrate tolerance illustrates that many of the consequences of obesity in man may be reproduced in experimental animals.[9]

Suitable bilateral hypothalamic lesions placed by electrolysis in the brain stem of rats or monkeys lead to the rapid development of an enormous degree of obesity. Rats weighing over 1,000 Gm. and macaques whose body weight increased from 3 to 18 Kg. in a few weeks may be produced by these means. The cause of the obesity is the intense voracity which develops just as soon as the lesions are made. These creatures

are short-lived, develop in many instances renal and vascular disease, and indeed furnish an interesting confirmation of the deteriorations of body function too frequently found in man as a consequence of excessive indulgence in food. A certain proportion of these obese animals develop a progressive impairment of carbohydrate tolerance which in the rat is noteworthy since in this species the pancreas is more resistant to insult than it is in others. If the pancreas of the rat has been partly removed, but not to an extent to cause glycosuria, the development of voracity and obesity that follows the placing of such brain lesions is at once reflected by the appearance of glycosuria. Of greater importance is the observation that after the obesity has persisted for a while, reduction of food intake to normal levels no longer brings about a disappearance of glycosuria. So far as it may be judged, the fat metabolism of these animals is normal and the conclusion is that the impairment of carbohydrate tolerance is a consequence of a relative insulin deficiency.

THE MAINTENANCE OF BLOOD GLUCOSE DURING FASTING

The importance of maintaining a minimal level of blood glucose, around 70 mg. per cent, during times when either no food is available or the diet contains no preformed carbohydrate is, in the higher forms of life, to be attributed to the obligatory requirements of the nervous system. An animal deprived of the capacity to maintain an adequate supply of glucose soon succumbs and death is to be attributed to the failure of this tissue only, since the other tissues of the body are able to exist when no glucose reaches them through the blood stream.

There are two ways by which the organism can maintain the blood glucose during such periods. The first is by its formation from non-carbohydrate precursors, largely proteins and their derivatives, the second by reducing the utilization of this substance to the minimal levels essential for the maintenance of the nervous system. Both mechanisms are available to the body and both are influenced by the endocrine system.

The chief clue to the nature of this control by the endocrine system is furnished by a comparison of the effects of fasting on normal and hypophysectomized animals. For example, a normal rat may fast for days without developing a serious degree of hypoglycemia, but the hypophysectomized animal succumbs in a period of hours. If simultaneous observations are made on the liver glycogen it will be found in hypophysectomized animals that as soon as this falls to the low levels characteristic of fasting, the blood glucose begins to fall. This does not occur in normal animals even when the liver glycogen is reduced to an equal degree, indicating quite clearly that the effect of the mechanisms responsible for stabilizing the blood glucose is greatly reduced in the absence of this endocrine gland. It may be said at this point that it is the loss of the anterior lobe of the hypophysis that is responsible for the effects observed.

Another striking difference in the behavior of normal and hypophysectomized animals is found in the effect of fasting on the muscle glycogen. In normal animals, even fasted to the point of death, the level of muscle glycogen—after an initial fall from the fasting level—is maintained. On the contrary, in hypophysectomized animals there occurs a rapid fall in muscle glycogen. This fall in muscle glycogen indicates an abnormally rapid consumption of carbohydrate during a time when, in normal animals, there is a minimal utilization of this substance. That there is a high consumption of carbohydrate is also suggested by the high respiratory quotient maintained by these animals during the fasting period.

The remarkable amelioration of pancreatic diabetes associated with removal of the anterior lobe of the pituitary is well known. In previous lectures it has been adequately discussed both by Professor Houssay, who first described this phenomenon, and by Professor Young. In the light of these results, however, it is interesting to point out that the metabolism of total diabetes and of normal individuals in the fasting state has many points of similarity. Indeed, in retrospect the effects of hypophysectomy on total diabetes might have been deduced by knowledge of its effect on fasting.

The similarities between the two are as follows: In both there is an increased rate of gluconeogenesis from protein, a decreased utilization of carbohydrate and an increased utilization of stored fat. The chief difference between the two is, of course, that in diabetes the blood glucose is excessively high while in fasting it is at the lower limit of normal. Hypophysectomy produces in both situations a fall in the fasting blood glucose, a decrease in gluconeogenesis during fasting, and an increased utilization of carbohydrate. Furthermore, the injection of crude extracts of the anterior pituitary not only exacerbates the mild diabetes of hypophysectomized-depancreatized animals, but also confers a normal resistance to fasting on hypophysectomized animals.

These experiments, although they do not allow an exact distinction to be made as to whether it is the

lowered rate of gluconeogenesis or an inability to reduce carbohydrate utilization that is responsible for the failure of the hypophysectomized animal to sustain a fast, or for the amelioration of total diabetes, at least clearly indicate that one or both of these processes is markedly influenced by the hormones of the anterior pituitary.

THE METABOLIC HORMONES OF THE ANTERIOR PITUITARY

The further analysis of the effects of loss of the anterior lobe on carbohydrate metabolism or those following injections of crude extracts of the gland is made difficult by the fact that this endocrine organ secretes at least six hormones. Those that have been well characterized as to their individual identity are the two gonadotrophic hormones, the thyrotrophic hormone, the adrenocorticotrophic hormone (ACTH), the lactogenic hormone, and the growth hormone.

The gonadotrophic hormones and the thyrotrophic hormone may be excluded from further consideration since removal of the gonads or the thyroid does not reproduce either sensitivity to fasting or any amelioration of total diabetes. In addition, the lactogenic hormone seems to be of little importance as a regulator of carbohydrate metabolism in the mammal, at least as judged by the failure of highly purified preparations to influence the blood glucose or the diabetes of the Houssay animal.

This leaves for further consideration ACTH and the growth hormone. Since the former can only influence metabolism by its capacity to increase the rate of secretion of adrenal cortical steroids, it is necessary before it, too, can be excluded to consider the influence of the adrenal cortical hormones on carbohydrate and protein metabolism.

THE ADRENAL CORTEX AND CARBOHYDRATE METABOLISM

It has been known for many years that both individuals suffering from Addison's disease and animals deprived of their adrenal glands frequently develop hypoglycemia. The susceptibility of adrenalectomized animals to the development of hypoglycemia during fasting, although not as marked as in the case of hypophysectomized animals, is nevertheless very evident. Furthermore, it is accompanied, at least in the fasting adrenalectomized rat, by a diminished rate of urinary nitrogen excretion. This is not due to a failing renal function since it is observed in animals receiving adequate amounts of sodium salts and water during the fast. Since the quantity of urinary nitrogen is a reflection of the amount of non-carbohydrate precursors available for the support of the blood glucose level, these results would indicate that in the adrenalectomized animal the development of hypoglycemia during fasting is in part due to the decreased rate of gluconeogenesis from the tissue proteins.

This concept is supported by the quantitative study of the effects of the injection of adrenal cortical extract or of steroids of the cortisone type into fasting adrenalectomized rats.[10] It is found that there is a significant elevation of blood glucose and a ten to twenty-fold increase in liver glycogen without any change in muscle glycogen. Consequently there must have occurred an accelerated rate of tissue protein catabolism and this is confirmed by the observation that there is an increased urinary nitrogen excretion during the injection period which is adequate to account for the new carbohydrate found in the body fluids and the liver.

It might be argued that the above experiment is merely another example of the efficiency of replacement therapy and affords no proof of the direct participation of adrenal cortical hormones in the gluconeogenetic processes. However, comparable injections of these hormones into normal fasted rats also is followed by an accumulation of liver glycogen and slight hyperglycemia, while there is a marked increase in urinary nitrogen excretion, again sufficient in amount to account for the extra carbohydrate found in the injected animals.

When hypophysectomized rats are injected during a period of fast with adrenal cortical extract, the blood glucose is maintained and the liver glycogen is increased. However, the increase in liver glycogen is much less than in normal animals, even though the urinary nitrogen increase is as great. At the same time, the low level of muscle glycogen found in fasting is not improved by treatment with cortical hormones. These two points of difference in the response of hypophysectomized animals, namely, a smaller increment in liver glycogen and a persistence of subnormal muscle glycogen levels, indicate that not all the defects in the fasting metabolism of hypophysectomized rats can be repaired by adrenal cortical hormones. Since the administration of crude anterior lobe extracts does restore the normal state, it would seem clear that not only is the ACTH content of these extracts required, but that some other anterior lobe factor is necessary for the establishment of the normal fasting metabolism. Some insight into the nature of this factor may be gained from the ob-

servation that a high rate of carbohydrate utilization still persists in fasting hypophysectomized rats treated with cortical hormones. This may be deduced from the smaller increment in liver glycogen and the persistence of subnormal muscle glycogen levels.

Nevertheless, there is little doubt that ACTH and the adrenal cortical steroids are major factors in enabling animals to maintain the level of blood glucose during fasting. They apparently accomplish this by accelerating the rate of protein catabolism and hence make available intermediary metabolites that are converted into liver glycogen. At the present time it is not known at what point in the chain of these reactions the hormones exert their effect. It could be either in the breakdown of the proteins to amino acids, the deamination of the amino acids, or at some point in the conversion of the carbon residues to liver glycogen.

The importance of a simultaneous depression of carbohydrate utilization and an increased rate of gluconeogenesis in maintaining the level of blood glucose has been pointed out above. The influence of adrenal cortical hormones on carbohydrate utilization in the tissues is most easily demonstrated in animals subsisting on a high carbohydrate diet since any changes are more easily detected. Under these circumstances it has been clearly demonstrated that the 11-oxygenated adrenal steroids or ACTH depress the utilization of carbohydrate and, if treatment is continued, cause a temporary diabetic state that is characterized by a marked resistance to the action of insulin.

It has already been pointed out that the similarities between the metabolism of fasting and that of total diabetes might have allowed a prediction to be made that since hypophysectomy modifies the response of the organism to fasting, it would also attenuate a total diabetes. Such a prediction was, of course, not made and it is only since the pioneer work of Houssay that we have come to appreciate the fact that the endocrine control of certain metabolic transformations manifests itself both in fasting and total diabetes.

The same hypothetical line of reasoning would also have led us to predict from the effects of adrenalectomy on fasting that this glandular deficiency would also modify a total diabetes. Certainly Lukens and I were motivated by other considerations when we carried out our experiments on the effects of adrenalectomy on pancreatic diabetes.[11] The intent we had then was to determine whether or not some of the effects of hypophysectomy were due to the atrophy of the adrenal cortices that was known to occur in animals after this operation.

The results obtained with cats and dogs, and later with rats, showed quite clearly that a very significant modification of the diabetes followed removal of all adrenal cortical tissue. This was particularly evident in the fasting state and was indeed comparable in degree to that observed after hypophysectomy in these species. It was later shown that ACTH preparations would exacerbate the diabetes of hypophysectomized-depancreatized animals, and that adrenal cortical hormones would exacerbate the diabetes of adrenalectomized-depancreatized animals. It was concluded that at least a part of the effects of hypophysectomy on diabetes were due to the inhibition of adrenal cortical secretion that follows the loss of the adrenocorticotrophic hormone. While it was tempting to assume that all the effects of hypophysectomy were due to this cause, it soon became apparent that this was not the case. Houssay and his colleagues, as well as the Yale laboratory, showed that if a crude extract of anterior pituitary is given to adrenalectomized-depancreatized animals, whether maintained on sodium salts or by small doses of cortical extract, there promptly occurred an increased degree of glycosuria. Since such animals could not increase their supply of cortical hormone, the only possible conclusion was that the anterior pituitary extracts contained another "diabetogenic" factor that exerted its effect independently of the adrenal cortex. This second factor is now believed to be the growth hormone.

THE EFFECT OF THE GROWTH HORMONE ON CARBOHYDRATE METABOLISM

A large part of the analysis of the effects of hypophysectomy on the metabolism of fasting or in diabetes has had to await the separation and characterization of the various anterior pituitary hormones. Consequently it was not until fairly recently that preparations of the growth hormone, essentially free from the other anterior lobe hormones, have become available for experimental purposes. This separation was accomplished first by Li[12] and at Yale by Wilhelmi, Fishman and Russell.[13] It was soon found, in confirmation of earlier work with impure preparations, that the injection of this hormone into fed animals not only brought about a marked retention of nitrogen (protein synthesis?) but, if continued, was followed by evidence of an inhibition of carbohydrate utilization. Up to the present time it has been found that growth hormone: (a) depresses the respiratory quotient of fasted hypophysectomized or fed normal rats, (b) prevents the severe loss of muscle glycogen observed when hypophysectomized animals are fasted, (c) depresses the glucose uptake

of the isolated diaphragm. In addition, when given to partially depancreatized rats or to animals made diabetic with alloxan, it causes a marked exacerbation of the diabetes. Finally, the diabetogenic potentialities of this hormone have been amply shown by the work of Houssay and Anderson,[14] Young and others[15] and Campbell and others.[16] All these have shown that the injection of total amounts of this hormone of the order of 10 to 20 mg. will produce permanent diabetes in dogs and cats. The production of permanent diabetes, as Young had previously shown with crude anterior lobe extracts, is undoubtedly due to the irreversible damage to the islets of Langerhans that is produced.

There is still much to be learned of the effects of growth hormone on metabolism. Since it is intimately related to one of the least understood metabolic processes, the synthesis of protein, it is likely that we shall have to await information on these processes before a more accurate analysis of its function can be given. For example, the relationship between its capacity to suppress carbohydrate utilization and to augment protein synthesis is signally obscure. Under certain circumstances it exhibits a *hypoglycemic* rather than a hyperglycemic action. For instance, when given to fasted animals the blood glucose soon falls to subnormal levels, an effect that may be related to the reduction of protein catabolism, and hence to a diminution in the quantity of carbohydrate precursors. Continued injection, as has been pointed out above, causes a reversal of this and the appearance of hyperglycemia. There are also still unsolved questions as to its effect on insulin secretion. The occurrence of hypoglycemia, after injection into normal fasted animals, may be due to a stimulation of insulin secretion while the increase in blood glucose of depancreatized animals may be due to their inability to secrete additional quantities of insulin.

This is perhaps the most interesting of all the anterior lobe hormones but time prevents further speculation on its role in the economy of the body. For the moment we must conclude that it is an agent that under certain circumstances can diminish the utilization of carbohydrate and hence serve to maintain the blood glucose level.

EPINEPHRINE AND CARBOHYDRATE METABOLISM

Twenty-five years ago a discussion of the endocrine factors regulating the blood glucose level would have centered largely around insulin and epinephrine. Today the importance of epinephrine in this regard has been largely supplanted by our new knowledge of the functions of the anterior pituitary and adrenal cortical hormones. Nevertheless, epinephrine is a hormone that is rapidly released under a variety of circumstances and which has the property of accelerating the rate of glycogen breakdown both in liver and muscles. In the former, glycogen is released to the blood stream as glucose, and in the latter largely as lactic acid which on reaching the liver is converted into glucose. The operation of this cycle enables the muscle glycogen to serve as an indirect source of blood glucose.

Until recently the action of epinephrine on carbohydrate metabolism was believed to be limited to its capacity to make available the preformed stores of carbohydrate in liver or muscle for the maintenance of the blood glucose. It has, however, now been demonstrated that epinephrine also brings about the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary.[17] While the mechanism of this effect of epinephrine on this gland is not completely understood, the fact that ACTH release does follow the release of epinephrine into the circulation is of some importance.

Perhaps the best example of the effects of this linkage between the adrenal medulla and the anterior pituitary is furnished by the response of the organism to hypoglycemia. In this situation the immediate restoration of the blood glucose level is essential for life.

It is well known, since the classical work of Cannon that, when the true blood glucose falls much below 50 mg. per cent, epinephrine discharge occurs as a consequence of the irritating effect of the low blood glucose level on the centers in the brain stem controlling its discharge. The epinephrine entering the blood stream not only accelerates the discharge of any preformed liver glycogen as glucose, but with equal rapidity evokes a release of ACTH from the pituitary. ACTH in turn releases additional quantities of adrenal cortical steroids, which as has been pointed out, have as one of their important metabolic effects the ability to accelerate the conversion of tissue proteins to liver glycogen. The liver glycogen formed from the breakdown products of the amino acids is then available to still further augment the blood glucose. In this way the rapid and a more slowly acting mechanisms for the support of the blood glucose level are effectively linked. It would appear that the ability of normal fasted animals with low levels of liver glycogen to recover spontaneously from moderate degrees of insulin hypoglycemia is due to their capacity not only to discharge the small stores of liver glycogen they possess, but to supply all the glucose they require for recovery by an acceleration of protein catabolism. When the blood glucose has thus been restored to

normal levels, the activity of both the adrenal medulla and the anterior pituitary is simultaneously suppressed.

CONCLUSION

I have endeavored to point out that while the absolute level of the blood glucose at any time is a resultant of those processes by which glucose is added to the blood and those by which it is utilized in the tissues, the maintenance of the blood glucose within the rather narrow limits found under normal circumstances is a consequence of a close interaction between those metabolic processes and the secretions of certain endocrine organs, notably those of the pancreas, anterior pituitary and adrenals.

The rate of utilization of glucose in the tissues, and hence the upper limit of blood glucose, is largely determined by an adequate secretion of insulin. There is valid evidence to support the view that insulin secretion is increased by a rising blood glucose level, a type of regulation that would appear to be admirably adapted to deal with the sudden entry of considerable quantities of glucose into the body.

On the other hand, the maintenance of a minimal level of glucose in the blood is the result of a complex interplay between the secretions of the anterior pituitary, the adrenal cortical hormones and, in some instances, the hormone of the adrenal medulla. This system supports the blood glucose in three ways. First, by the discharge of epinephrine which makes available any preformed liver glycogen. Second, by the release of ACTH, which in turn augments the secretion of the 11-oxy adrenal steroids, one function of which is to accelerate glucose formation from non-carbohydrate precursors. Third, another effect of these steroids appears to be a suppression of carbohydrate utilization by the tissues. In this they may be reinforced by the anterior pituitary growth hormone, or possibly by another still unidentified hormone from this gland. While the mechanism that is responsible for the stimulation of anterior lobe function during fasting is obscure, there is little doubt of its occurrence; in the absence of this organ the blood glucose soon declines to levels incompatible with life.

The new knowledge, on the role of the anterior pituitary and adrenal glands in the regulation of carbohydrate metabolism, contributes to our understanding of human diabetes by throwing light upon the chain of events that is unleashed when the insulin supply becomes deficient. While it has not yet given us as clear an insight as we would wish into the reasons why the disease occurs in man, it is not too much to hope that as our knowledge of the basic activities of these hormones and their interrelation to each other unfolds, there will be revealed to us the reason for the high incidence of human diabetes.

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THE PROPER USE OF

Laboratory Tests

IN THE DIAGNOSIS AND MANAGEMENT

OF DIABETES

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A well-balanced index of suspicion of diabetes is essential to the physician in internal medicine or general practice. As one sees the kaleidoscopic range of disease, the possibility of diabetes should be rapidly, routinely and reflexly considered in dealing with persons in the following categories: all those who have diabetic relatives, the obese, and those with conditions which place a burden on the function of insulin. A suspicion should lead to investigation by laboratory tests.

FACTORS PREDISPOSING TO DIABETES

Examination of the urine for sugar is particularly valuable in the febrile patient. Infection is nature's sugar tolerance test; in many instances fever taxes the function of insulin far more than 100 Gm. of glucose. The alert physician will, therefore, use these occasions to make his routine urinalysis for sugar. If negative, the patient probably has a good insulin reserve. If positive, one must suspect and usually treat as diabetes, establishing the severity of the disease later by appropriate study.

Part of the mechanism which makes fever antagonistic to insulin is the activation of the adrenal cortex. The proper examination of the urine for sugar during the treatment with ACTH and cortisone may well reveal a number of prediabetics. Endocrine diseases, such as hyperthyroidism, acromegaly, and Cushing's syndrome, have a high incidence of diabetes. Repeated examinations for diabetes are part of the management of such patients.

Finally, whenever one encounters a condition which might be a complication of diabetes, the minimal screening tests are indicated. The following conditions are especially noted—arteriosclerosis of the feet (this may appear before glycosuria and is most common at the age when the incidence of diabetes is high), gallbladder

disease, cataract and retinitis, coronary disease and hypertension. In all these cases, a blood sugar test should be made in addition to routine urinalysis.

If physicians were to watch their patients with a reasonable index of suspicion of diabetes, there would be many fewer cases found by Diabetes Detection Drives and life insurance examinations.

TESTS FOR SUGAR IN THE URINE AND THE BLOOD

With this brief reminder of what may make the physician think of diabetes, the next question that arises is: What laboratory tests should be used for diagnostic screening? For the busy physician these must be simple. The routine urinalysis will suffice in most cases, if the specimen of urine is obtained an hour or more after a meal. If the test is positive, a blood sugar test is required. Where conditions that might be complications of diabetes are found, a blood sugar test, in addition to the urinalysis, should be routine. The blood sugar test should be made one to two hours after a meal.

At this point, a word is in order about false or misleading laboratory tests. If the urine specimen cannot be tested immediately, a preservative should be added, especially in warm weather. I have found 4 plus sugar in testing urine immediately after voiding, although the same sample tested the following day has been reported negative. The morning specimen of a patient with mild diabetes may be negative, although a test made after a meal will show sugar. For routine tests, choose the time when the suspected diabetic is most likely to have glycosuria.

Nondiabetic glycosuria is encountered in a group of rare conditions. For practical purposes, they are eliminated by a blood sugar test; the blood sugar is normal. It must be emphasized that renal glycosuria, pentosuria, and the other melituria are rare in comparison to diabetes mellitus. It is wise to act on the rule that "glycosuria always means diabetes until proved otherwise." A blood sugar test should be made in order to determine its significance.

The levels of blood sugar deserve comment. The Council of the American Diabetes Association has endorsed the use of the blood sugar values shown in Table 1 in the diagnosis of diabetes. For a flat diagnosis this is fine, but in recent years I have become suspicious of any fasting blood sugar above 100 and of any value above 140 after meals. A single report at such a level does not warrant the diagnosis of diabetes, but it merits repetition within a month or two. As an illustration, two patients were referred with severe diabetes; two years previously they had had single fasting blood sugar values of 110 and 115, while hospitalized for surgical treatment. These values were textbook normals and nothing more was said or done. How much better one would feel, if these patients had been rechecked in some way. Checking would show an alert attitude to such laboratory reports.

What confirmatory examinations should be made when these initial tests are borderline? These will be indicated by the individual situation. If a decision must be made immediately because of consideration for life insurance or management during pregnancy, or difficult surgery, a sugar tolerance test at once may be in order. In many instances, the repetition of urine and blood sugar tests at times when the patient is to be seen for some other condition may answer the question as well or better. Three or four normal blood sugar tests a year for several years will do more to exclude diabetes than any one test. When the blood sugar is normal, tests should be carried out to identify the type of sugar in the urine, but it is more important to be sure that one is dealing with a nondiabetic glycosuria than to classify the type of nondiabetic melituria.

GLUCOSE TOLERANCE TESTS

In the normal adult given 100 Gm. of glucose by mouth, the venous blood sugar usually rises no higher than 200 and returns to 120 or less in two hours. An elevation of the fasting value or a value above normal at two hours is strong evidence for diabetes. The height or peak of the blood sugar curve at one-half or one hour has limited significance. For this reason, almost everyone has abandoned the one-hour two-dose sugar tolerance test and has returned to the original type of test, in which the blood sugar curve is followed for two or three hours. If the observations are extended for five or six hours, sugar tolerance tests may be of some value in the diagnosis of spontaneous hypoglycemia. The intravenous tolerance test is useful because it excludes changes which might be related to defects in gastrointestinal motility and absorption, but it is still used principally as a research procedure.

The need for preparation of the sugar tolerance test should be emphasized. The patient should have been on a normal type of diet, relatively high in carbohydrate, for three days or more before the test. The test should not be made immediately on any individual who has been treated for diabetes, either with insulin or with restriction of the carbohydrate of the diet. Starvation

or even low-carbohydrate consumption in advance of the test may result in a high blood sugar curve which may even simulate the response of the diabetic.

It is not necessary to perform a sugar tolerance test when the fasting blood sugar is high. This, if confirmed, establishes the diagnosis of diabetes. A sugar tolerance test is a diagnostic aid when other blood sugar values are indecisive. But borderline or bizarre curves are often found in doing tolerance tests. Blood sugar values below the diabetic levels (Table 1), especially normal fasting blood sugar values, do not exclude diabetes. At times a diabetic may have a normal blood sugar both before and after eating, if the diet has been restricted or insulin has been taken before the test. On the other hand, a nondiabetic person may have hyperglycemia and glycosuria after previous starvation.

TABLE 1 Diabetes is present with a high degree of probability when the blood sugar is more than:
(All values in mg. per 100 ml.)

Source of blood	Folin-Wu Method		Somogyi Method	
	Fasting	After meals	Fasting	After meals
Venous	130	200	110	150
	Folin-Malmros Method			
Capillary	140	240	120	200

From: Diabetes Guide Book for the Physician, American Diabetes Association, 1950.

Quantitative determination of glucose in a 24 hour specimen of urine is rarely employed in diagnosis. It may be useful when glycosuria is present with normal blood sugar levels. When the glycosuria represents only a few grams in 24 hours while the patient is on an ample diet and when the blood sugar level is normal, it supports the diagnosis of nondiabetic glycosuria.

Until one is familiar with the patient, the presence of sugar in the urine should always lead to a test for ketonuria (the nitroprusside or ferric chloride test). When acetonuria is present, acidosis will be suspected and the carbon dioxide combining power of the serum should be determined to complete the picture. Acetonuria makes one think at once of acidosis, infection and the need for more insulin.

USE OF LABORATORY TESTS IN GUIDING THE TREATMENT OF DIABETES

Chemical tests should be selected according to the needs of the patient and according to the standard of control desired by the physician. The restoration of the diabetic patient to a normal state of metabolism would require that the urine be kept free from sugar and that the blood sugar be kept normal. Some physicians strive to reach this ideal in all of their cases, others feel satisfied to disregard glycosuria and hyperglycemia, while still others strive for normal tests in certain cases, yet are satisfied with less than perfection in control in other cases. In any case, one factor which influences the choice of laboratory tests is the degree of control reached by the patient at the moment.

Simple laboratory tests help in the estimation of the amount of insulin needed. These include qualitative tests for sugar in the urine, made on fractional specimens of the daily urine output, quantitative urinary sugar examinations on measured specimens, and blood sugar tests. Except in cases of severe diabetes, tests of samples of urine collected four times a day, for example at 7:00 and 11:00 a.m., and 4:00 and 9:00 p.m., provide a satisfactory guide to treatment. The usefulness of this method must not blind one to its limitations. The results may be misleading when there is a wide range of change in the rate of excretion of urine, and in the total volume output. In spite of these objections, the proper use of these serial qualitative tests can give valubale information. They show when qualitative control of glycosuria is being reached, and they also show the time of day when more insulin is needed. Furthermore, if the tests show that for fourteen to eighteen hours of the day there is no glycosuria, one can conclude that control has progressed fairly well.

Quantitative examinations on the excretions of sugar for all or part of the day are useful at times. They reveal the true meaning of qualitative glycosuria which resists the usual methods of control. In juvenile or unstable diabetics, and in diabetics whose diet and insulin have been made irregular because of surgery or complicating disease, it is often helpful to know the amount of carbohydrate utilized. If the estimated intake of sugar exceeds the excretion of sugar in the urine by 100 Gm. or more, the patient can be considered safe, except in unusual circumstances. Further adjustment of the diabetic's regimen can be made after the complication has subsided. When I see a labile diabetic whose daily glycosuria varies from 5 to 80 Gm. on a constant hospital regimen and when the quantitative test shows that on the average enough glucose is utilized to maintain health, I cease to scold the patient for the qualitative glycosuria which is found on office visits.

Blood sugar determinations aid in more accurate control after the urine is largely sugar free. A single blood sugar may be regarded as a one-minute point on a 24 hour curve. In practice, only occasional blood sugars at selected times are required for most diabetics. As a rule,

blood sugars are taken to learn the highest and lowest levels reached during the day. The exact times of interest to the physician will depend upon the particular dose and type of insulin in use.

In the early stages of the management of diabetes, few blood sugar tests are needed while glycosuria persists; glycosuria itself shows that the blood sugar is 200 or more. After glycosuria has been controlled, the blood sugar determination should be checked again. Tests should be made not only in the early-morning fasting, but at various times during the day—for example, the late forenoon and late afternoon.

A word is in order concerning the instruction of patients in the use of laboratory tests. Most well-educated diabetics have learned one of the tests for glycosuria (Benedict's, Clinitest, Galatest, etc.). The physician must direct the use of the test at home. Usually, the urine samples desired by the physician should be tested one day a week. Where there is any question of infection, reaction or other irregularity, special tests may be performed by the patient. However, it is important not to make the diabetic a "laboratory invalid" and, therefore, home testing should be kept at a proper minimum. At present, the test for acetone (Acetone Test powder is available for patients' use) deserves to be used more often. All diabetics ought to make the test at the onset of every intercurrent illness, reporting positive tests to their physicians. It should be pointed out, though, that the nitroprusside reaction is sensitive, and slightly positive tests may have no clinical significance.

If, in spite of large doses of insulin, the 24 hour specimen of urine cannot be kept sugar free, one may be dealing with diabetes of great severity or great instability. There may be peaks of hyperglycemia when glycosuria may be found, while at other times there may be hypoglycemia and insulin reactions. It is obvious that the determination of any single blood sugar will be an uncertain guide to regular treatment. Here the quantitative determination of the urine sugar in a 24 hour specimen is a valuable guide. If the excretion of glucose is small, one can conclude that an adequate amount of carbohydrate is being utilized by the patient. If, for example, a patient is using a diet containing 160 Gm. of glucose and has a total of 20 Gm. of glucose in the urine, this leaves a balance of 140 Gm. of carbohydrate utilized. If the patient's weight and strength are satisfactory, he may safely continue to live with this balance, with confidence that the glucose utilization is adequate to maintain good nutrition. Continued efforts may be made to improve matters by reaching the desired state of freedom from glycosuria.

CONCLUSION

Chemical tests measure silent symptoms which should be interpreted as wisely as other symptoms. The life of the diabetic individual should be improved and not made miserable by these diagnostic and therapeutic guides. Patients must be neither frightened nor neglected, but they must be encouraged to follow the path of discipline which leads to health.

THE INCIDENT OF THE INVOLUNTARY SHOPLIFTER

Medical evidence is not always so readily accepted in a court of law as it was in the case reported in the *Manchester Guardian* of July 20, where a married woman had been charged with shoplifting. It was alleged that she took a "sunsuit" from a rail in a store, put it underneath her coat, and left the shop without paying for it. She later said to the police: "It was a stupid thing to do. I don't know what made me do it. I had money to pay for it."

The defense before the Sheffield magistrates was that the accused had been dieting under doctor's orders and had carried her treatment too far. A medical practitioner stated that, as the result of her blood sugar reaching an abnormally low level after dieting, she was acting automatically and had suffered a lapse of consciousness, similar to that of a man who is kicked on the head during a game of football but continues to play without remembering afterwards what he has done. The magistrates dismissed the charge; if there was no criminal intent there could be no conviction; they obtained from the accused's husband an undertaking that she would discontinue her dieting.

—Lancet, *August 4, 1951.*

Hyperglycemia in Coronary Thrombosis

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The frequent association of hyperglycemia and coronary thrombosis has long been recognized. However, the significance and pathogenesis of this finding, and the possible relationship to diabetes mellitus have been obscure. The present study was undertaken in an attempt to clarify the problem.

PREVIOUS LITERATURE

In 1929, Levine[1] noted glycosuria in 23.7 per cent of his 145 cases of coronary thrombosis. This series included known diabetics. He mentioned, however, that in one-fourth of these patients the glycosuria was transitory and present only during the acute phase of the vascular occlusion. Eckerstrom[2] reported a transitory hyperglycemia or glycosuria of short duration in 36 of 69 non-diabetic patients with coronary thrombosis. The blood sugar values were almost always less than 200 mg. per cent. Gottsegen[3] described a patient who developed moderate hyperglycemia and glycosuria coincidental with coronary thrombosis. These abnormalities gradually disappeared, but recurred with succeeding episodes of myocardial infarction.

In 1936, Raab and Rabinowitz[4] reported a study of glucose tolerance in patients with coronary thrombosis. They found the tolerance curves to be abnormal in 100 per cent of their cases when the test was performed within two weeks after the attack. When the occlusion had occurred many months before the test, 67 per cent of the curves were normal. They concluded that the disturbed carbohydrate metabolism was unrelated to latent diabetes and suggested that the abnormalities resulted from a disturbance of the vegetative nerve centers of the brain. Spuhler[5] noted the presence of hyperglycemia and glycosuria at the onset of coronary thrombosis. He reported that the elevated blood sugar seldom reached 200 mg. per cent and that the values tended to return to normal by the end of the first week. Goldberger and others,[6] on the other hand, found that in 11 cases in which the glucose tolerance test was performed

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within two weeks of the thrombosis, only 4 curves were abnormal, and all fasting blood sugars were normal; further, they found that in these 4 and in 1 case in which the curve had been normal, diabetes eventually occurred.

Most recently Eckerstrom,[7] in a study of over 200 cases of acute coronary occlusion, reported the presence of transitory hyperglycemia in over half of the nondiabetic patients. Glucose tolerance curves, however, yielded normal values, which indicated that the hyperglycemia was not a manifestation of underlying diabetes. Follow-up studies in 12 of these patients as long as 10 years after the coronary occlusion still revealed the presence of normal glucose tolerance curves and the absence of diabetes.

STUDY OF 75 CASES OF CORONARY THROMBOSIS

Our approach to this problem was through the correlation of clinical observations and postmortem findings. Only cases proven by autopsy were included in this study. Seventy-five consecutive autopsied cases of coronary thrombosis were studied from the following points of view: (1) the presence of hyperglycemia or glycosuria, (2) clinical evidence or history of diabetes, (3) evidence of shock, (4) sex and age, (5) presence and extent of congestive heart failure, (6) electrocardiographic findings, and (7) necropsy findings.

The cases studied were divided into two main groups. Group 1 consisted of all the known nondiabetics and those having neither history, clinical manifestations, nor postmortem findings suggestive of the disease. Group 1 was further subdivided into cases with hyperglycemia and those who had normoglycemia. Group 2 comprised the patients with diabetes mellitus.

In Group 1, hyperglycemia was considered to be present when the fasting venous blood sugar was 130 mg. per cent or more. In only one case was the blood sugar more than 200 mg. per cent (230 mg. per cent); in all other cases it ranged from 130 to 185 mg. per cent, the average being 160 mg. per cent. Twice there was an associated glycosuria. There were 15 such cases (20 per cent). There were 45 cases (60 per cent) with normoglycemia and no glycosuria.

TABLE 1 SEX DISTRIBUTION

	No. of Patients	Male	Female
Diabetes	15	6 (40%)	9 (60%)
Nondiabetic hyperglycemia	15	11 (73%)	4 (27%)
Normoglycemia	45	30 (67%)	15 (33%)

All the categories were compared with respect to age and sex distribution. There was no significant difference in age, most of the patients being in the seventh decade. An analysis of the sex distribution is shown in Table 1. The normoglycemic group shows the usual male preponderance in patients with coronary thrombosis, whereas the diabetic group shows the expected excess of females. Of particular note, however, is the increased frequency of the male sex in the nondiabetics with hyperglycemia.

OBSERVATIONS IN NONDIABETIC CASES

To present more clearly certain impressions, the nondiabetic will be considered separately from the diabetic cases.

In all cases, clinical evidence of diabetes, retinopathy or Kimmelstiel-Wilson lesions was absent.

A comparison of the clinical findings revealed distinct differences between the patients who had hyperglycemia and those who had normoglycemia. Most striking was the presence or absence of shock. Shock —as determined by the usual clinical criteria of a fall in blood pressure, rapid thready pulse and cold clammy extremities—was present in all but 1 (93 per cent) of those showing elevation of the blood sugar, whereas it appeared in more than transitory form only twice (4 per cent) in the normoglycemic group (Table 2). Shock in the hyperglycemic group was usually profound and always of some duration. As further evidence of the difference in severity between the two groups, the clinical course of the hyperglycemic patients was stormier and their average survival time was only 6.3 days as compared with a survival time of 20.3 days for the normoglycemic group. The electrocardiogram revealed a much higher incidence of conduction pathway defects and arrhythmias in the hyperglycemic group. There was no significant difference in the incidence or severity of congestive heart failure.

Clinically, then, the differences between these two groups were indicative of a more severe involvement in the hyperglycemic group, with the oustanding feature being the presence of profound and prolonged shock in those with hyperglycemia.

Postmortem studies also showed significant differences between these two groups. The infarcted area of the heart tended to be more extensive in the hyperglycemic group. More striking, however, was the presence of central liver cell necrosis in the cases that had shock (Table 2). Thirteen of the 15 patients with hyperglycemia had central liver cell necrosis, whereas only

2 of the 40 normoglycemic patients showed liver cell necrosis and 1 of these was focal rather than central. Liver cell necrosis was diagnosed when the following criteria[8] were satisfied: (1) congestion of the central vein and distention of the sinusoids in the central area; (2) eosinophilic staining of the involved area, contrasting sharply with the basophilic stain of the normal liver cells; (3) nuclear changes consisting of pyknosis, disintegration, fading nuclei, or occasional nuclei lying free of the cytoplasm; (4) polymorphonuclear leukocytic infiltration; and (5) architectural disruption (Figures 1 and 2).

TABLE 2

	Shock (per cent)	Central Liver Cell Necrosis (per cent)	Survival (days) Time
Normoglycemia	4	4	20.3
Hyperglycemia	93	87	6.3

The relationship of central liver cell necrosis to the presence of prolonged shock has been demonstrated in a previous publication.[8]

It would seem that the hyperglycemia is the clinical accompaniment of shock, whereas the liver cell necrosis is its morphological manifestation. In view of this clear clinical background and associated pathology, it seems unnecessary to consider these patients as having latent diabetes. The sex distribution and the complete lack of any evidence suggesting diabetes conform with this interpretation.

An appraisal of reported experimental and clinical observations lends confirmation to our findings and support to the shock mechanism as the explanation of the hyperglycemia. Extensive biochemical changes have been noted repeatedly in experimentally-induced shock in animals. The most significant fact in all such studies has been that these alterations are entirely independent of the exciting cause of the shock, be it thermal burns,[9] mechanical trauma,[10] hemorrhage,[11] or anoxia.[12] Further, the extent of chemical alteration has seemed proportional to the severity of the shock. In addition to hyperglycemia, observed changes have included lactacidemia, a rise in blood pyruvic acid content, a lowered carbon dioxide content, a rise in the blood amino acid concentration, and increased urinary nitrogen.

A similar, though far less extensive experience has been encountered in human beings. Taylor and others,[13] found such biochemical changes in thermal burns. The extent of the changes was roughly proportional to the extent and severity of the burn. Davidson and others,[14] investigated chemical changes occurring in the blood in patients with "medical shock." They found a clear relationship between the presence of peripheral vascular failure and the appearance of hyperglycemia, lactacidemia and lowered carbon dioxide content. These findings, as in the animals, were entirely independent of the factors precipitating the shock syndrome. The latter included such differing etiologies as pyopericardium, barbiturate poisoning and dissecting aneurysm of the aorta. On the other hand, those of their patients who did not develop shock failed to show similar changes.

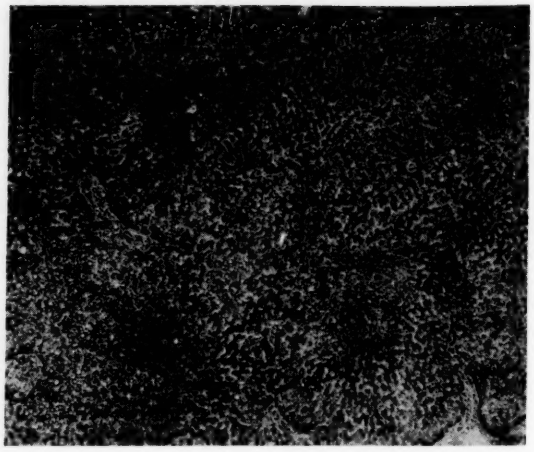

FIGURE 1. Low-power microscopic view showing areas of central liver cell necrosis.

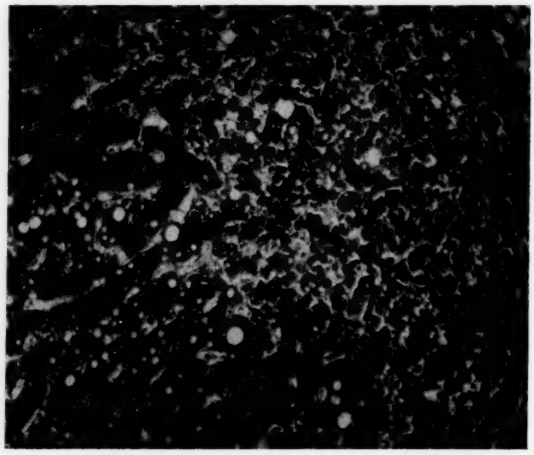

FIGURE 2. High-power view. Note sharp line of demarcation between necrotic and normal liver cells, leucocyte infiltration and staining differences.

The nature of the relationship between hyperglycemia and shock has been a matter of much conjecture. On the basis of present knowledge, the hyperglycemic response may be attributed to a combination of two mechanisms. The initial and immediate hyperglycemia results from a sharp increase in hepatic glycogenolysis mediated, in all probability, via an outpouring of epinephrine by the adrenal medulla, under the stimulus of shock-producing factors. Evidence for this lies in inhibition of this reaction in adreno-demedullated animals and in starved animals.[15] Further evidence is afforded by the demonstration of an increased glucose content of the hepatic vein[16] and the demonstration that an intact sympathetic nervous system is necessary for the production of the hyperglycemia.[11]

There must be another mechanism that maintains the hyperglycemia since it continues long after the liver glycogen has been depleted. This probably consists of an increase in gluconeogenesis since there is an associated increase of cortin-like substances in the urine, presumably related to adrenal cortical activity. As shock continues and the associated anoxia is accentuated, its effects are intensified. There is a progressive shift to the anaerobic mechanism of carbohydrate metabolism accompanied by an increase in blood lactate and pyruvate. The liver being particularly susceptible to oxygen deprivation, its ability to remove these substances and amino acids decreases. There then ensues an even further rise in lactate, pyruvate and amino acids.

In keeping with the observed metabolic aberrations and their relationship to shock are the pathologic changes in the liver. Central liver cell necrosis has been correlated with the presence of shock in trauma,[17, 18] in medical cases,[14] and in burns;[19] indeed, this finding has been shown to be related only to the presence of prolonged shock, regardless of the precipitating causes of the shock.[8] This fact is readily explained by the vulnerability of the liver to oxygen lack. Because of the dual nature of its blood supply, the liver is poorly fortified against abrupt changes in circulatory dynamics. In general, the anoxia resulting from shock is combatted by vasoconstriction. Such constriction, however, if sufficiently intense and prolonged, may lead to tissue necrosis. Penner and Bernheim[20] demonstrated acute necrosis in the upper as well as the lower gastrointestinal tract, resulting from severe, prolonged vasospasm.

One may conjecture that the central liver cell necrosis we have observed results from shock, the accompanying anoxia, and the compensatory vasospasm. It is suggested that the sequence of events in the production of hyperglycemia in these cases of coronary thrombosis is as follows: (1) the insult of the occlusion results in severe shock; (2) there is an immediate outpouring of epinephrine, which stimulates hepatic glycogenolysis; (3) as shock continues, the adrenocortical mechanisms come into play and a sharp increase in gluconeogenesis results; (4) vasospasm is active and produces local anoxia; (5) prolonged vasospasm and anoxia disrupt the normal hepatic functions and eventually lead to central liver cell necrosis. Obviously, this is a crude picture and there undoubtedly are many accompanying changes, though probably similar in nature and origin. Support is found for this suggested mechanism in the fact that we have demonstrated marked and relatively persistent eosinopenia in clinical studies of coronary thrombosis.[21]

If this is correct, the following statement would hold: Hyperglycemia is a clinical manifestation of shock, and central liver cell necrosis is an anatomical manifestation of shock.

OBSERVATIONS IN DIABETIC CASES

If the shock attending coronary thrombosis is the cause of hyperglycemia in nondiabetics, one would anticipate a marked alteration of carbohydrate metabolism in diabetics under comparable conditions because (1) abnormal carbohydrate metabolism already exists and (2) it is an old clinical observation that coronary thrombosis in diabetics tends to be more severe than in nondiabetics.

Fifteen patients of the total series were known diabetics. Of these, 11 had shock; 4 did not have shock. This is a higher incidence of shock than in the nondiabetic group. The 11 patients with shock had a stormy course and the average survival time was only 5.6 days, the shortest of all the groups.

From the point of view of carbohydrate metabolism, all 11 cases in which there was shock showed a definite increase in the severity of the diabetes, as measured by the presence of ketosis, definite increase in fasting blood sugar or insulin requirement. In 8 of the 11 patients there was acetonuria, graded from 1 plus to 4 plus, and lowering of the carbon dioxide combining power as far as 22.6 vol. per cent. The accompanying blood sugar concentration ranged from 215 to 445 mg. per cent. In the 3 cases without acetonuria the blood sugar was above 300 mg. per cent and in 1 of these cases insulin was required for the first time in 4 years. In contrast with this picture, the 4 diabetic cases without shock did not show any alteration in carbohydrate metabolism.

The postmortem findings were of interest. In the 11 diabetic cases with shock, central liver cell necrosis was found in 9; in the other 2 cases death occurred too soon to permit the development of this phenomenon. The pathologic alterations were identical in nature with the central liver cell necrosis observed in the nondiabetic cases in which there was hyperglycemia and shock. In the 4 diabetic cases without shock central liver cell necrosis was not present at autopsy (Table 3).

TABLE 3 CASES OF DIABETES

	No. of Patients	Diabetes Worse (per cent)	Liver Cell Necrosis (per cent)
Shock	11	100	81
No shock	4	0	0

It appears that shock is the cause of an increase in the severity of diabetes in coronary thrombosis, and that the shock is reflected in central liver cell necrosis pathologically. This is similar to the mechanism that alters the carbohydrate metabolism in nondiabetics and indicates that this change is independent of the diabetes per se.

CONCLUSIONS

1. Hyperglycemia occurring in acute coronary thrombosis is a manifestation of shock and is accompanied by central liver cell necrosis.

2. Diabetes does not play any role in the occurrence of the hyperglycemia.

3. The mechanism of increased severity of the diabetes in cases with coronary thrombosis is identical with the mechanism of hyperglycemia in nondiabetics with coronary thrombosis.

The authors acknowledge with thanks the assistance, guidance and material made available by Dr. Paul Klemperer.

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DISCUSSION

DR. SAMUEL SOSKIN *(Chicago, Ill):* The authors have shown an appreciation of the role of the liver in carbohydrate metabolism and the fact that it is upon the liver that the various endocrines play in regulating the blood sugar level. Certainly, their explanation of the immediate effects of shock are logical in accordance with our knowledge of physiology, and there would seem to be little reason to doubt that the adrenal cortex plays a role in maintaining the hyperglycemia when it is great or prolonged.

This paper calls to mind what has been termed "traumatic diabetes," referring to those apparently authenticated cases in which diabetes has appeared for the first time after trauma or shock. In some of these cases one can secure information about a diabetic family history or the presence of potential diabetes previously, but in many cases it is not possible to discover such a background.

Our definition of diabetes is more or less limited by the fact that we can make this diagnosis with certainty

only when there is *persistent* hyperglycemia with glycosuria. There is a number of conditions causing temporary hyperglycemia with glycosuria, which we cannot call diabetes. I think the viewpoint and the conclusion of the authors are fully justified.

DR. J. E. SEXTON *(Champaign, Ill.):* Do you have statistics on the incidence of coronary thrombosis in your cases of diabetes as compared to a control group?

DR. WILLIAM S. COLLENS *(Brooklyn, N.Y.):* Some 25 years ago, while working in the Cornell Department of Physiology, I performed ligations of the hepatic artery in dogs and produced a histological picture comparable with what you saw here today. These dogs developed central hepatic necrosis in spite of the fact that only 25 per cent of the total blood supply to the liver was embarrassed. Death in hypoglycemic convulsions occurred within 50 hours after the operation. At the same time, the glycogen in the liver disappeared.

I should like to ask the authors if they repeated the blood sugar determination at later periods and if any observations of fasting blood sugars were made within 24 hours of death?

DR. MAX ELLENBERG (Closing): In response to the first question, I have no statistics except that of these 75 unselected cases, 15 had clinical evidence of diabetes, whereas the other 60 were nondiabetic.

With reference to Dr. Collens' remarks, I am familiar with his excellent work in showing the development of the central liver cell necrosis resulting from the anoxia which followed the ligation of the hepatic artery. I did not have time to mention the pertinent references in the literature.

We did not have any blood sugar determinations within 24 hours before death except in those cases in which death occurred 24 to 48 hours after the onset of the acute coronary thrombosis. These showed hyperglycemia.

So far, we have not had any opportunity to observe what happens to the blood sugar immediately prior to death. The mortality in our experience has dropped almost to zero, but the hyperglycemia that we have been able to demonstrate in cases of shock is of relatively short duration and the blood sugar has usually returned to normal by the end of the fifth day following the onset of the coronary thrombosis.

A requisite virtue for the Inquiring Physician as he pursues his clinical research is that of sustained enthusiasm. Too much of the world's work today is being done by grumbling artisans who rarely, if ever, have experienced the emotional glow that goes with the a job well done. One of the most devastating sentences in the English language is to be found in Thoreau's *Walden,* "The mass of men lead lives of quiet desperation." But the Inquiring Physician, with a deep and abiding passion for his work, will find that his enthusiasm is sustained through failure as well as success. His efforts will not be motivated by academic honors or prizes, nor by public acclaim. These are but by-products of the deeper yearning for the inner peace that comes to a man who has had work to do and who knows himself when it is accomplished that he has done it well. And when he reaches the end of the road, may he have the equanimity of soul that buoyed up the great Laennec as he lay dying of tuberculosis at the age of forty-five. He had published his monumental treatise on auscultation, which was met with ridicule and contempt on the part of his contemporaries. It is stated that he received only two letters of praise from the medical world for his effort. But he was still able to say, "I shall consider ample, yea more than sufficient reward for my labor, if it should prove the means by which a single human being is snatched from untimely death."

—From "The Inquiring Physician," by Wesley W. Spink.
Journal of Laboratory and Clinical Medicine, *January 1951.*

Dermal Reactions to Insulin Therapy

One of the earliest papers on insulin therapy by Banting and his colleagues[1] described a slight induration of the subcutaneous tissue and reddening of the skin immediately surrounding the point of injection. At this time Joslin and his co-workers[2] stated that induration had been seen frequently at the site of insulin injections and described four cases of urticaria developing among the first 83 diabetic patients treated. Later, redness and swelling were observed to follow the injection of protamine insulin,[3] and similar reactions have been described following the use of globin insulin.[4]

The wide variation in the reported incidence of local skin reactions, as shown in Table 1, may be due in part to the differences in the thoroughness with which the investigators have looked for local sensitisation. The higher incidence since 1936 can also be related to the greater frequency of reactions to protamine insulin used since that time. Cutaneous reactions to insulin therapy may occur in nondiabetic patients. Blotner[5] treated 100 patients suffering from malnutrition with insulin and recorded an incidence of 31 per cent. Since no uniformity of opinion exists with respect to the incidence, nature, and treatment of local cutaneous reactions to insulin, the subject will be reviewed in the light of our experience at Leeds.

CLASSIFICATION OF DERMAL REACTIONS

Lawrence[6] described the local effects of insulin injection as "immediate" and "delayed." The delayed reaction was a hot, brawny swelling appearing at the site of injection about the third to fifth day of treatment, being fully developed in 6 to 12 hours and disappearing in 24 to 36 hours. The reactions became less intense after 7 to 10 days and usually disappeared in 2 to 3 weeks, but in some instances remained for 3 months.

Allan and Scherer[7] investigated the nature of the local allergic phenomena to insulin in a series of 100 sensitive patients. Their classification amplified that given by Lawrence[6] and has been further modified to describe the lesions observed in our studies.

1. *Mild Local Reaction*
   - A. Immediate
     - (1) Stinging on injection. This is by no means an invariable occurrence.
     - (2) Swelling and redness appear 1-2 hours after injection.
     - (3) Area of reaction 1-4 cm. in diameter.
     - (4) Maximum intensity 12-24 hours after injection.
     - (5) Disappears in 1-3 days.
   - B. Delayed

     Similar to the immediate reaction, but onset delayed 6 to 24 hours after injection.
2. *Severe Local Reaction*
   - A. Immediate
     - (1) Observed within 1 hour of injection.
     - (2) Area involved may extend to 15 cm. in diameter.
     - (3) Usually disappears within a week.
   - B. Delayed

     Identical with previous reaction, but onset delayed 6 to 24 hours after injection.

TABLE 1 INCIDENCE OF SKIN REACTIONS TO INSULIN IN VARIOUS COUNTRIES

Year	Author	Country	Incidence of Reactions (per cent)
1922	Joslin, Gray, Root (2)	U.S.A.	5.0
1925	Lawrence (6)	Great Britain	30.0
1925	Strauss (54)	Germany	5.0
1927	Allan, Scherer (7)	U.S.A.	3.2
1928	Allan, Scherer (7)	U.S.A.	5.2
1929	Allan, Scherer (7)	U.S.A.	13.8
1930	Allan, Scherer (7)	U.S.A.	8.0
1931	Allan, Scherer (7)	U.S.A.	14.1
1934	Collens, Lerner, Fialka (47)	U.S.A.	7.3
1936	Grafe (55)	Germany	5.0 (approx.)
1938	Blotner (5)	U.S.A.	31.0
1946	Joslin (16)	U.S.A.	15.0 to 30.0

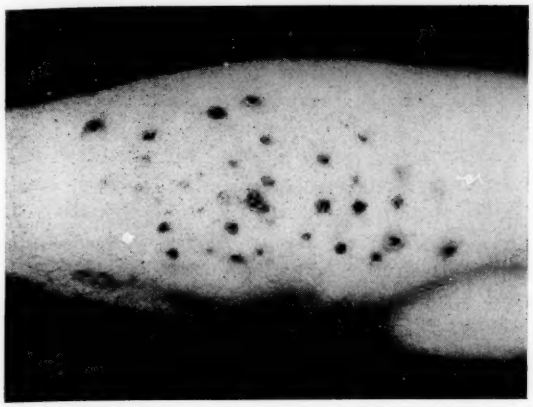

FIGURE 1. Various stages of pseudo-reactions to insulin at an area used for its injection.

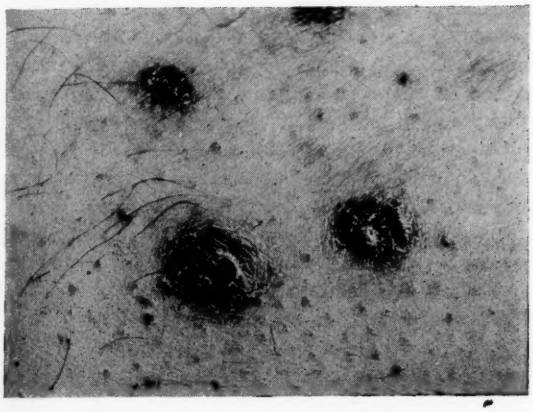

FIGURE 2. Pseudo-reactions to insulin. (Close-up.)

FIGURE 3. Suppurative and ulcerative lesions associated with the administration of insulin. Photograph kindly supplied by Professor D. M. Dunlop.

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3. *Generalized Reaction*

This serious form of sensitivity to insulin has not been encountered during the present investigations. It is extremely rare.[8]

4. *Pseudo-Reaction*

This reaction has not been described previously. Marked pain during and after each injection was experienced. A circumscribed swelling with blanching of the skin appeared almost immediately after injection. The areas involved varied from 1 to 4 cm. in diameter. The lesions became reddish in color approximately an hour later and then slowly developed a violaceous hue. These reactions have been extremely indolent, with slight superficial necrosis and scab formation (Figs. 1 and 2). Wilder and others[9] described suppurative and ulcerative lesions occurring after insulin therapy, and Dunlop[10] has reported a patient with similar lesions, (Fig. 3), who was receiving globin insulin. When regular insulin was injected no lesions appeared. The cause did not seem to be intradermal injections since globin insulin given by deep subcutaneous injection produced exactly the same reactions. In our experience no pus and no frank slough has appeared in the pseudo-reactions although there has been superficial loss of tissue with minor scarring. Careful observation showed that the lesions were caused by our patients giving all or part of their daily injections intradermally. As soon as insulin was given into the subcutaneous tissues, pseudo-reactions ceased to appear. In one patient no further trouble was experienced; with two patients typical local skin reactions continued.

INCIDENCE

In the Diabetic Clinic of the General Infirmary at Leeds 55.8 per cent of 147 patients, who started therapy in the years 1947 to 1949, developed cutaneous reactions.[11] Of these patients, a larger proportion of females (65 per cent) than of males (26 per cent) suffered reactions. This difference was significant. Only one other author has noted this sex differential with respect

to dermal reactions.[6] However, it has been recorded repeatedly with respect to fat atrophy following insulin injections.[12-14]

As Table 1 shows, the incidence of all reactions varies greatly. The incidence of the various types of reaction, however, has shown no major difference when compared with the data presented by Allan and Scherer[7] (Table 2).

TABLE 2 INCIDENCE OF EACH TYPE OF SKIN REACTION

		Per cent	Authors Paley (11)	Allan and Scherer (7)
Mild local reaction	Immediate	74.4	81.7	84.0
	Delayed	7.3		
Severe local reaction	Immediate	17.1	18.3	12.0
	Delayed	1.2		
Generalized reaction		0.0	0.0	4.0

Kern and Langner[3] stated that the local reactions to insulin were usually accompanied by burning and itching. Stinging at the site of injection has not been an invariable phenomenon in our series and only occurred in 60 per cent of patients. The incidence of stinging was, however, significantly greater in patients experiencing dermal reactions than in those with no such reactions.

Typical local sensitivity to injections of protamine zinc insulin, has been reported;[3, 15] Joslin[16] considered the local responses have been more common since the introduction of protamine zinc insulin.

In our experience dermal reactions occurred in 66 per cent of cases treated with protamine zinc insulin, but in only 27 per cent of cases given regular insulin.

TIME OF ONSET AND DURATION

References to the time of onset and duration of skin reactions have been few.[17, 18] We found the mean time of onset was 13 days from the first injection. The local irritation from insulin appeared, during the first week, in 61 per cent of cases, in the second week in 18, in the third week in 12 and in the fourth week in 9 per cent.

No patient was seen to react with the first injection of insulin, but 22.4 per cent of sensitive patients had local reactions following their second injection. The mean time of onset for the mild immediate local reactions in 41 patients was 15 days and for the severe immediate local reactions in 17 patients was 9 days. The difference was not significant. The duration of reactivity was known accurately in only 35 sensitive patients and showed a mean interval of 212 days. The shortest period was 38 days and the longest 546 days. The duration of reactivity in the patients with mild and with severe local reactions was essentially the same.

ANALYSIS OF POSSIBLE FACTORS RESPONSIBLE FOR DERMAL REACTIONS

Previous History of Allergy. Allergic states such as asthma, hay fever, migraine, are uncommon among diabetic patients.[19, 20] Kern,[21] reviewing 300 diabetic patients, obtained a positive history of allergy in 20.3 per cent (61 patients), but the allergic manifestations had ceased in 46 of the 61 patients prior to the onset of diabetes mellitus. In our series only two patients presented some allergic manifestations while under treatment for diabetes mellitus, but both, one with giant urticaria and the other with migraine, had suffered from these disorders for many years. A review of our patients showed that previous attacks of urticaria or constitutional dermatoses[22, 23] such as infantile eczema, seborrheic eczema, rosacea and psoriasis did not appear to make them more prone to local insulin reactions.

Several authors[16, 24, 25] have recorded eosinophilia in diabetic patients (based on differential cell counts) and have suggested that the increase in eosinophils was due to insulin therapy. In a study of the incidence of eosinophilia in diabetic patients[26] no significant difference was found between the direct eosinophil counts in patients treated on diet alone and patients treated with diet and insulin. The severity of the local reaction to insulin did not affect the degree of eosinophilia: patients suffering from mild local reactions gave a mean eosinophil count of 143.7 cells per mm^3, and patients suffering from severe local reactions gave a mean eosinophil count of 137.7 mm^3. These findings did not support the contention that insulin-treated diabetic patients developed an eosinophilia.

Faulty Technique. Allan and Scherer[7] reported skin reactions in one of their patients due to hypersensitivity to the formalin contained in the denatured alcohol used for storing the syringe. Storage and sterilization of the syringe and needles, as well as injection technique, were carefully checked for all our patients and the injection of denatured alcohol could not be implicated.

Preservative. Several workers have attributed dermal reactions to the preservative used in insulin manufacture.[2, 19, 27] Insulin manufactured in America usually contains phenol as preservative, although o-cresol is used by at least one manufacturer. In Great Britain cresol

B.P. (tricresol) or o-cresol is used. The probable reason for the use of o-cresol is that it is a pure chemical substance, whereas cresol B.P. may contain varying concentrations of different phenols.

Hydrogen Ion Concentration. The acid reaction of insulin solution,[28, 29] and the salt content of the pancreatic extract[1] have also been considered to be responsible for the reactions.

The main method of investigation of all the above factors has been the intradermal injection of substances contained in insulin preparations which were thought to be irritative. There have been few references to the time and method of reading the reaction. Friedlander and Feinberg[30] used histamine as a test solution in human subjects and read the reaction 15 minutes after the injection, whereas Leavitt and Gastineau[27] used insulin and read the reaction after intervals of 5 and 10 minutes. In our investigations we have given a test injection of 0.02 ml. intracutaneously and 15 minutes was found to be the optimum time for reading all test reactions.

Using this technique, Paley[31] showed that sensitive diabetic patients reacted to a test injection of buffer solution (pH 3.0-3.2). This effect was *reduced* by adding 0.3 per cent of cresol B.P. to the buffer. A solution of insulin at pH 3.0-3.2 with 0.3 per cent cresol B.P. caused a significant increase in area of reaction. A comparison of the intradermal reactions obtained with insulin solutions, containing respectively cresol B.P. and o-cresol, revealed no significant difference.

INSULIN

No difference in the incidence of skin reactions was observed in 72 sensitive diabetic patients receiving three standard British manufactured protamine zinc insulins, all prepared from beef pancreas. In a further 28 sensitive patients the brand of insulin was changed at random without previous intracutaneous testing and none lost sensitivity with this maneuver. It has been shown that the incidence of reactions was greater in patients treated with protamine zinc insulin than in those treated with soluble insulin alone, suggesting that the protamine might play a part in producing the reactions. Page and Bauman[29] showed that protamine was irritating. About 19 per cent of their diabetic patients gave a positive reaction to intracutaneous injection of protamine solution. On the other hand, Kern and Langner[3] noted no positive test when their group of patients was injected intracutaneously with a protamine solution, containing 0.1 mg. of nitrogen per ml. Recently it has been shown[31] that salmine sulphate (0.052 per cent solution), injected intracutaneously, had no irritant effect on the skin. Furthermore, the mean area of reaction to the intracutaneous injections of commercial protamine zinc insulin was 430.1 mm^2, which corresponded closely to the figure obtained from the injection of commercial soluble insulin, *viz.* 456.9 mm^2.

All British commercial insulins are prepared from crystalline insulin, but the possibility that "secondary protein" (species protein) may be carried over in the preparation and included in the final product could not be excluded. When commercial soluble insulin was recrystallized six times, a strikingly significant reduction in mean area of reaction was observed.[11] The difference in mean areas of test reactions between commercial and recrystallized insulin was 237.5 ± 52.9 mm^2. A more marked difference was observed between the test reaction from insulin recrystallized six times and insulin currently used by our patients, *viz.* 484.9 ± 56.1 mm^2.

The striking reduction in the area of reaction after the use of six times crystallized insulin suggests that the major factor in the production of the dermal responses is closely associated with insulin. Hult and Jorpes[32] using insulin recrystallized seven times came to the same conclusion and described a number of patients who required specially purified insulin. Approximately 300 sensitive patients in Sweden have received purified insulin and the majority have been relieved of local reactions.[33]

NATURE OF THE "DERMAL REACTING FACTOR" IN INSULIN

In the early days of insulin therapy, animal experiments were employed in an attempt to solve the nature of the local and general skin reactions.

Raynaud and Lacroix[34] obtained serum from a patient with anaphylactic symptoms to insulin and with this serum sensitized a guinea pig. When the guinea pig received an injection of insulin from the phial used by the patient anaphylactic shock occurred. They further demonstrated the presence of precipitins to insulin in the patient's serum. Tuft[35] confirmed their work and stated that antibodies other than precipitins were not demonstrable. It has been shown that purified insulin was a different antigen from that of serum or of pancreatic proteins.[36] Wassermann, Broh-Kahn and Mirsky[37] published data indicating that insulin was weakly antigenic, but stressed that the results might be due to the presence of impurities. If crystalline insulin has the

same chemical composition and structure as that produced by human pancreas, then local skin reactions would not be expected to occur following its use. Sanger[38] has shown that there are certain distinct differences in the detailed chemical structure of insulin in different animal species. The significance of these differences in the chemical composition of insulin with regard to the production of dermal reactions has not yet been assessed. Species differences in the chemical composition of insulin will not, however, explain all the facts. In our studies, British insulin has been used entirely and this is manufactured from beef pancreas alone, so that the factor of species differences did not occur. It would seem more likely that impurities possibly of a protein nature were responsible. Sutherland, Cori, Haynes and Olsen[39] have undertaken electrophoretic studies of insulins, using the Tiselius apparatus. They investigated (a) an amorphous insulin, (b) a crystalline zinc insulin, and (c) a Novo preparation, using an acetate buffer of ionic strength of 0.1 and at a pH of 3.8. On the ascending side of the electrophoretic pattern a small but very slowly moving peak was observed with all three insulins; but with the amorphous and crystalline insulins a small peak was observed just behind the main protein component and no such peak was observed with the Novo preparation. They suggested that the small peak behind the main component might be identified as the hyperglycemic fraction originally described by Burger[40] and calculated that it composed about 10 per cent of the soluble protein. These authors also found that Danish Novo insulin failed to produce initial hyperglycemic reaction when administered intravenously to intact animals and failed to cause increased glycogenolysis in liver slices.

The residue obtained from the mother liquors after recrystallizations of an insulin was concentrated and a solution prepared. Intravenous injections of this impure fraction, and of various insulins shown to produce skin reactions in sensitive diabetic patients, into fasting rabbits failed to reveal a hyperglycemic factor.[41]

All the available evidence suggests that the principal factor or factors responsible for the dermal reactions are related to the protein character of insulin or associated impurities. The fact that in rare instances reactions were obtained with test solutions which did not contain insulin suggests that in these patients there were specific local factors which are not called into play in the majority of individuals. The low incidence of allergic manifestations, normal eosinophil count and absence of a definite sensitizing period support the view that the dermal reactions to insulin are a local response to a product in the solution and not a true allergic manifestation. No workers have as yet succeeded in associating the dermal reacting properties with a specific impurity or with a specific source of insulin.

TREATMENT

It has been shown that even when the greatest care is exercised in injection techniques and in sterilization, more than 50 per cent of the patients on insulin therapy have experienced dermal reactions. In the majority, however, these reactions disappeared within three to six months of the onset of treatment and therefore have not called for an elaborate method of specific desensitization such as that described by Bryce[42] and others.[43-46] In the light of present knowledge this method and also that of non-specific desensitization[47-49] appear to have a very limited application. Several workers have reported satisfactory responses to the anti-histamine drugs, diphenhydramine hydrochloride (benadryl hydrochloride)[50] and pyribenzamine hydrochloride.[51] The authors have found "Anthisan," when mixed with insulin, reduced the severity of the sensory disturbances but produced no significant reduction in the area of reaction.

Goldner and Ricketts[52] stated that intramuscular injections of insulin partially alleviated the local reactions, but did not completely prevent symptoms. During our studies intramuscular injections have been tried, but without any dramatic effect apart from those patients exhibiting pseudo-reactions. Insulin should be given in widely scattered sites in all diabetic patients. This applies even more to sensitive patients, since injections given into recent sites will boost the skin reactions.

Recently Dolger[53] has shown that merely boiling insulin appears to destroy the dermal reacting factor. Insulin treated in this way alleviated local reactions in five sensitive patients.

Fortunately, the demand for a highly purified and extremely costly insulin is not necessary for the routine treatment of diabetes mellitus. On no occasion during the present study has the use of highly purified insulin been required for the treatment of severe local reactions. Patients experiencing this type of local sensitivity were tested intradermally with different batches of three commercial insulins. The one giving a minimal test reaction was continued therapeutically until spontaneous desensitization occurred, whereafter the patients were able to tolerate any brand.

SUMMARY

Dermal reactions occurred in 55.8 per cent of patients receiving insulin while attending the Diabetic Clinic

at the General Infirmary at Leeds, 1947-1949. Eighty-two per cent of the reactions were mild and 18 per cent severe. A higher proportion of patients developed local reactions during the first week of treatment than in any subsequent weekly period. No predisposing clinical condition was found either at onset of diabetes or in the previous history to account for the occurrence of sensitivity.

None of the accessory factors, such as technique of injection, pH of solution, preservative, or salmine sulphate, appear to exert any constant irritant action in the skin. However, purified insulin, recrystallized six times, caused a significant reduction in the mean area of reaction when compared with soluble insulin.

Spontaneous disappearance of the lesions occurred in the majority of patients. The various forms of treatment previously advocated are reviewed.

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(Continued on page 40)

SERUM AND URINARY PROTEINS IN

Diabetic Glomerulosclerosis

RESULTS OF ELECTROPHORETIC ANALYSIS

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Since the original description of diabetic intercapillary glomerulosclerosis by Kimmelstiel and Wilson[4] in 1936, numerous reports have confirmed its existence as a specific clinical and pathologic entity. Although the fully established syndrome is well known to the trained clinician, one must be constantly on the alert for variants in the clinical picture. The presence of doubly refractile lipoid elements in the urinary sediment is an important aid in the diagnosis, provided it is properly related to the clinical data.[11] Study of the serum proteins may furnish additional laboratory evidence.

Although the clinical and pathologic findings in diabetic glomerulosclerosis are now well delineated, the pathogenesis of the lesion is poorly understood. McManus has demonstrated, by means of the Periodic acid-Schiff reagent, that the hyalin material in the glomeruli in diabetic glomerulosclerosis is a carbohydrate-containing protein.[9] It has also been postulated that increased circulating serum polysaccharide may be casually related to this renal lesion of diabetes mellitus.

In this study an electrophoretic analysis of the serum and urinary proteins has been undertaken. A special emphasis has been placed upon the alpha-2 globulin fraction since this has the highest polysaccharide content in normal serum[16] and has been reported[15] as varying directly with the serum polysaccharide content.

MATERIAL AND METHODS

Electrophoretic analyses were carried out on the sera of 10 patients and the urines of 3 patients with the fully established clinical syndrome. The analyses were done in veronal buffer, at pH 8.6 and ionic strength 0.10. The serum samples were diluted to 2 per cent protein before dialysis. The urine samples were not diluted, but were dialyzed extensively against saline prior to dialysis against the veronal buffer.

RESULTS

The electrophoretic patterns obtained on the sera and the urines of 3 representative patients are shown in Figure 1, and the analytical results on these same cases

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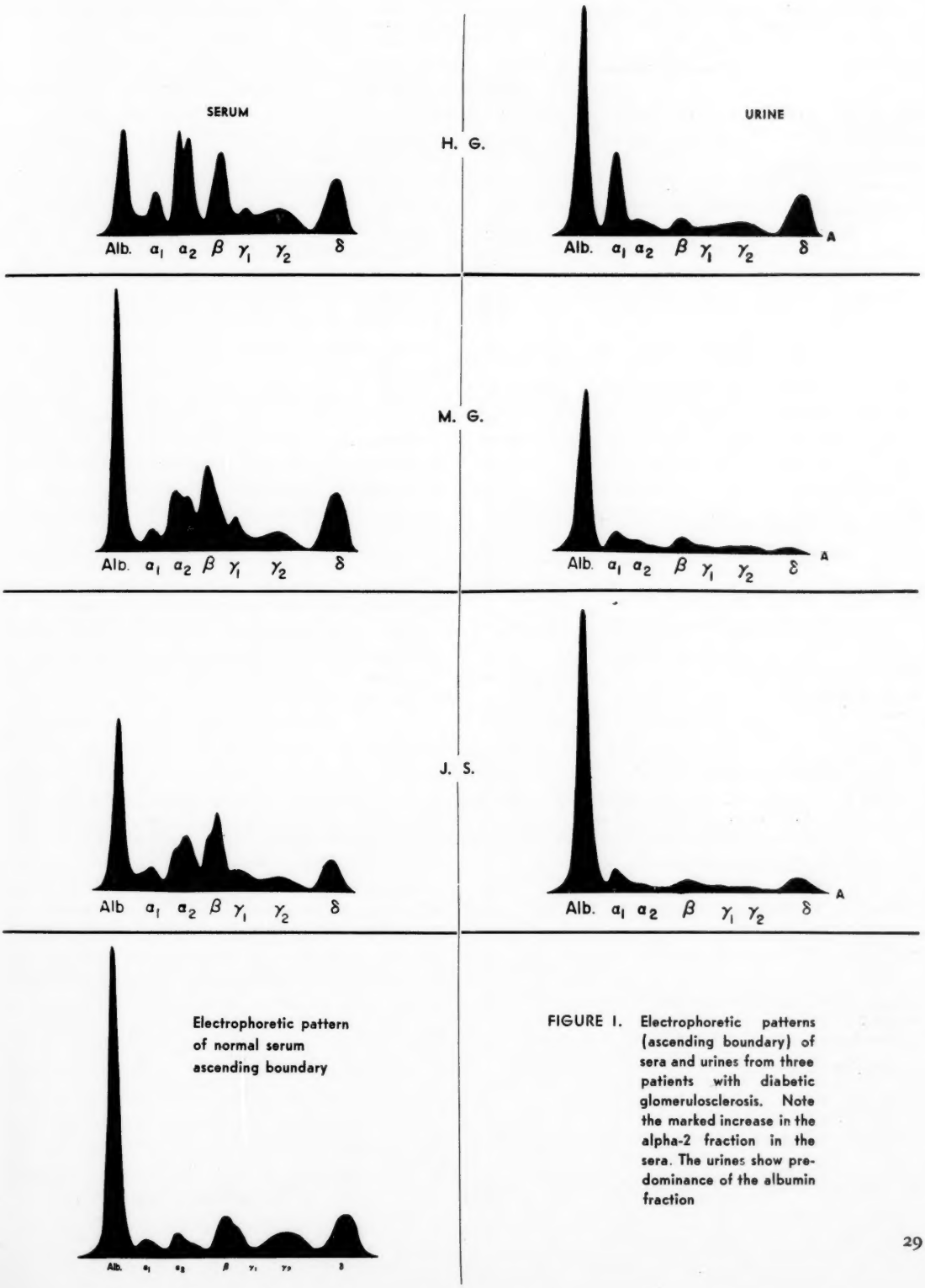

Electrophoretic pattern of normal serum ascending boundary

FIGURE 1. Electrophoretic patterns (ascending boundary) of sera and urines from three patients with diabetic glomerulosclerosis. Note the marked increase in the alpha-2 fraction in the sera. The urines show predominance of the albumin fraction

TABLE 1 Analytical results of the serum and urinary protein from three representative cases of diabetic glomerulosclerosis. Compare these results with the values obtained in normal healthy subjects

	Total Protein	Albumin	Globulin				
			$Alpha_1$	$Alpha_2$	Beta	$Gamma_1$	$Gamma_2$
	GRAMS PER 100 cc.						
Normal subjects Range (serum)	6.31-7.97	3.35-4.35	0.28-0.62	0.53-0.81	0.63-1.18	0.20	0.49-0.87
Patients with diabetic glomerulosclerosis							
H.G.—Serum	5.1	1.11	0.56	1.45	0.99	0.30	0.69
Urine	1.9	0.99	0.42	0.17	0.11	0.05	0.17
M.G.—Serum	6.6	2.52	0.38	1.38	1.21	0.51	0.60
Urine	0.8	0.52	0.08	0.07	0.06	0.02	0.05
J.S.—Serum	6.0	2.24	0.46	1.19	1.25	0.41	0.47
Urine	0.9	0.67	0.08	0.05	0.05	0.02	0.03

are given in Table 1. The sera from all 10 patients revealed a decrease in albumin, with a marked elevation of the alpha-2 globulins. An extra boundary between the beta and gamma globulins was noted in the serum of 3 patients, the mobility of which was close to that reported for gamma-1 globulin (sometimes called beta-2 globulin). Alpha-1 and gamma-2 globulins were within the normal range. The beta-globulins were either within normal limits or slightly elevated, as might be expected in diabetes mellitus.[5, 8, 15]

The urinary proteins consisted chiefly of albumin; in contrast to the results of the serum analyses the distribution of urinary globulins showed a predominance of the alpha-1 type.

Six of the 10 patients have now come to autopsy and the diagnosis of diabetic glomerulosclerosis has been confirmed. The 3 patients whose electrophoretic patterns are noted in Figure 1 are included in this group. As a control group, the sera of 5 patients with diabetes mellitus and hypertensive cardiovascular disease, but without the other clinical features suggestive of diabetic glomerulosclerosis, were studied. Electrophoretic analysis revealed either a normal or slight decrease in the albumin fraction with normal alpha-2 globulins and a slight increase in the beta globulin, which is the usual picture in uncomplicated diabetes mellitus. Postmortem examination of 3 of these patients revealed no evidence of the specific renal lesion.

TABLE 2 Contrast the electrophoretic analysis of the serum protein in the nephrotic phase of glomerulonephritis and in diabetic glomerulosclerosis. Although the $alpha_2$ globulin is elevated in both groups, the gamma globulin in contrast to the normal concentration in diabetic glomerulosclerosis is markedly reduced in nephrotic glomerulonephritis

Case	Cholesterol**	Urinary Protein***	Total Serum Protein*	Serum Albumin*	Serum Globulin			
					$Alpha_1$*	$Alpha_2$*	Beta*	Gamma*
Normal subjects (Range)			6.31-7.97	3.35-4.35	0.28-0.62	0.53-0.81	0.63-1.18	0.49-0.87
Nephrotic nephritis								
Case 1	985	14.5	5.3	1.38	0.42	1.16	1.59	0.26
Case 2	430	8.1	5.6	2.06	0.62	0.84	1.23	0.16
Diabetic glomerulosclerosis								
Case 1	620	13.5	5.1	1.11	0.56	1.45	0.99	0.69
Case 2	390	7.0	6.0	2.24	0.46	1.19	1.20	0.52

*Grams/100 ml. **Mg./100 ml. ***Grams/24 hours

DISCUSSION

The findings noted here differ significantly from those reported in diabetes mellitus without the specific renal complication. Electrophoretic patterns of sera from patients with mild untreated diabetes[14] reveal a normal distribution of protein although the total proteins are slightly decreased. Following therapy on a standard diet with not more than 80 Gm. of protein, the plasma proteins revert to normal. In patients with uncomplicated diabetic acidosis, an elevation in beta globulin occurs,[14] which is probably due to an increase in beta lipoproteins.[1] Electrophoretic analysis of the plasma proteins of patients with diabetic retinitis has been reported to show a low plasma albumin with a high beta globulin.[14] Although proteinuria and hypertension were noted in a number of these patients, it is not possible to determine from the data whether any of the patients had a true Kimmelstiel-Wilson syndroms. This is an important point since the electrophoretic data have to be interpreted in the light of the exact diagnosis. It should be recalled that all of our patients presented a composite picture of diabetes, edema, hypertension, combined diabetic and hypertensive retinopathy, severe proteinuria, and doubly refractile lipoid cells in the urinary sediment.

The electrophoretic pattern described for diabetic glomerulosclerosis differs from that obtained in most acute and chronic disease states, which show an increase in both alpha-1 and alpha-2 globulins with a decrease in the serum albumin. [3, 5, 8, 17] In our cases, the alpha-1 globulins were within the normal range.

The results appear somewhat similar to the electrophoretic analysis of the serum proteins in the well-developed nephrotic phase of glomerulonephritis.[5, 6, 8, 18] Here, too, there is a marked decrease in serum albumin, associated with an increase in the alpha-2 and beta globulins. The gamma globulin, however, in contrast to the normal concentration in diabetic glomerulosclerosis, is markedly reduced in nephrotic glomerulonephritis (Table 2). It is possible that the elevation of the alpha-2 globulin noted in both of these renal diseases is the result of a mobilization of protein reserves as in starvation,[17] and not due to the disease process.

Our patients were all in the sixth and seventh decades of life. It is important, therefore, that electrophoretic studies be repeated on young diabetic patients with the specific renal lesion. There is hope that further observations may prove of value both in the diagnosis of early cases of diabetic glomerulosclerosis, and in the differential diagnosis from coexisting diabetes mellitus and hypertensive cardiovascular disease.

SUMMARY AND CONCLUSIONS

1. In each of 10 patients with diabetic glomerulosclerosis, there was a significant elevation in the serum alpha-2 globulin.

2. Since in diabetes mellitus, uncomplicated by the specific renal lesion, the alpha-2 globulin is within normal limits, the possibility is suggested that the determination of the alpha-2 globulin may prove to be of value in the diagnosis of diabetic intercapillary glomerulosclerosis.

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DISCUSSION

DR. LOUIS LEITER *(New York):* The great interest aroused in recent years by the so-called degenerative vascular lesions of prolonged diabetes has coincided with a revival of careful clinical and pathological studies of the renal complications of diabetes. As a result, it is now clear that the diabetic patient in the course of years faces a number of renal hazards, of which diabetic glomerulosclerosis may be the most serious. Its clinical manifestations, including the specific urinary findings which Dr. Rifkin has mentioned, readily distinguish it from the acute glomerulonephritis or pyelonephritis likely to occur in the younger diabetic subjects, and from chronic pyelonephritis and the hypertensive renal vascular disease so common in the diabetics of the older age groups. However, difficulties in the differential diagnosis of diabetic glomerulosclerosis do arise: first, in younger age diabetics who may have nephrotic or hypertensive stages of chronic glomerulonephritis; second, in the older age diabetics who have proteinuria and renal insufficiency associated with congestive heart failure and renal vascular disease.

The increase in the serum alpha-2 globulin described by Dr. Rifkin will probably help in the differential diagnosis of diabetic glomerulosclerosis in this older age group from renal vascular disease in patients who have proteinuria and congestive heart failure. Unfortunately, alpha-2 globulin is also elevated in cases of nephrotic glomerulonephritis.

It should also be noted that along with the increase in beta globulin and fibrinogen, the alpha globulins are elevated in normal pregnancy, usually by the third trimester and continuing on through the first two weeks of the postpartum period. Whether this rise has implications as to the site of protein regeneration or is related to the endocrine disturbances in pregnancy is not known. Whether the alpha-2 globulins of nephrotic nephritis and in diabetic glomerulosclerosis are different or distinguishable from the normal alpha-2 globulins, electrophoretically or otherwise, remains to be determined.

An important question arises: Does the increase in alpha-2 globulin merely follow prolonged proteinuria or does it represent an early, perhaps primary, change in the serum protein pattern of the patient with diabetic glomerulosclerosis? If the latter alternative holds, then we may have a valuable tool for an early diagnosis of the specific diabetic renal lesion.

At present the evidence is too tenuous to warrant any conclusion as to a pathogenic relationship between increases in alpha-2 globulin and serum polysaccharides and the deposition of the polysaccharide containing hyalin material in the glomeruli of diabetic glomerulosclerosis.

DR. HOWARD F. ROOT *(Boston, Mass.):* The idea long established, that the so-called Kimmelstiel-Wilson lesion is peculiar to mild diabetes in middle and late life and unrelated to severity of diabetes, is not supported by observation of patients whose diabetes began early in life. Those of us who see diabetic children and young patients after twenty years of diabetes recognize the diabetic nephropathy, which includes the Kimmelstiel-Wilson lesion, arteriolarsclerosis and chronic pyelonephritis as the most common single cause of death. I would offer the conclusion that this lesion is really directly related to the severity of the diabetes, its duration and the character of its control.

DR. HAROLD RIFKIN (Closing): This renal lesion may certainly be associated with diabetes in young people, and we urge you to obtain electrophoretic analyses in these cases.

Controlled Versus Free Diet Management of Diabetes

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THE GEORGE F. BAKER CLINIC, ELLIOTT P. JOSLIN, M.D., MEDICAL DIRECTOR
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Clinical experience has led the authors to believe that continuous aggressive treatment of diabetes, directed toward the maintenance of physiologic conditions including normal levels of blood sugar, is of the greatest importance in reducing the incidence and severity of degenerative complications. *Ideal* control implies that a quantitated diet providing ample minerals, vitamins and calories derived from the proper distribution of carbohydrate, protein, and fat has been so well utilized by adequate insulin effect that blood and urine tests for sugar are invariably normal. Although this ideal is rarely attained, a consistent, conscientious effort to reach it will usually result in reasonably good control. On the other hand, in recent years some have advocated plans of treatment which provide much less rigid control and thus by the authors' standards fall far short of being adequate therapy for diabetes.[1-6] These plans allow, in general, a free selection of diet as well as disregard of glycosuria and hyperglycemia as long as acidosis is absent.

CLASSIFICATION OF CASES ACCORDING TO TREATMENT

The correlation between the degree of control maintained and the incidence and severity of degenerative vascular complications was recently determined in more than 300 youthful patients with diabetes of more than 10 years' duration, who were recalled to the office or hospital for observation and examination.[7] Two hundred and twenty-one of these cases have been divided into three groups, according to the degree of control maintained and the type of treatment followed in the management of their diabetes. All patients who had actually followed the type of careful treatment recommended to them by the authors were considered together as a group representing "controlled" treatment (73 cases). A second group, hereafter referred to as the "coma" group, included all patients who had been in diabetic coma on one or more occasions, regardless of the cause of coma or the degree of control maintained at other times (48 cases). The third group was

Presented at the Annual Meeting of the American Diabetes Association, Atlantic City, June 10, 1951. Based on data also published in *The Journal* of the American Medical Association, December 15, 1951.

composed of those patients (100 cases) who, despite advice to the contrary, had on their volition followed a "free diet" regimen of management similar to that advocated by Tolstoi and others.

With few exceptions, the patients in the "coma" group had had consistently poor control of diabetes. None of the 100 patients in the "free diet" group had ever been in coma or severe acidosis, as determined by review of their clinical and laboratory records covering many years of office and hospital visits. Each of the above three groups was further subdivided according to whether diabetes had been present for 10 to 15 years, 15 to 20 years, or 20 to 34 years.

INCIDENCE OF DIABETIC COMPLICATIONS

After the patients had been grouped according to type of treatment and duration of diabetes, an attempt was made to determine the relative incidence and severity of the two most commonly observed vascular complications of diabetes which can be objectively evaluated, namely retinopathy and calcification of peripheral arteries. Depending upon the findings of certified ophthalmologists as to retinal changes, the patients were grouped into five grades—from normal through grade 4. Similarly, the x-rays of all patients were evaluated and graded (normal through grade 4) according to degree of vascular calcification observed in roentgenograms of the aorta, pelvis, and legs.

Since 10 to 15 years of diabetes are usually required for the development of vascular degenerative lesions regardless of the type of management,[8-10] a true picture of the relationship in diabetic patients between the type of management followed and the complications resulting therefrom can be obtained only from those patients who have had the disorder for 15 or more years.

Among the 92 patients who had had diabetes for more than 20 years, 74 per cent of those in the "coma" group were found to show arterial calcification of an advanced degree, as did 80 per cent of those who followed a "free diet" regimen. In contrast, only 44 per cent of patients in the controlled group showed advanced blood vessel calcification, despite 20 or more years of diabetes. A similar correlation was noted between the incidence of advanced degenerative retinal lesions and the various degrees of control of diabetes. A greater incidence of retinopathy was noted after 15 years of diabetes among the patients in the "coma" and "free diet" groups than was found among patients in the controlled group.

When the incidence and severity of both retinopathy and vascular calcification were jointly correlated with the type of management of diabetes, the occurrence of complications in relation to degree of control became even more obvious. Among the 92 patients with diabetes of 20 to 34 years' duration, advanced lesions of both the blood vessels and eyes were observed more than twice as frequently in the "free diet" and "coma" groups (57 and 65 per cent of cases, respectively), as they were in the controlled group (25 per cent of the cases). Only 7 per cent of patients on a free diet regimen for 20 or more years were found to have minimal vascular complications as compared with 41 per cent of patients with controlled diabetes. No patient whose diabetes had been managed on a free diet regimen for 20 or more years had both normal retinae and blood vessels without evidence of calcification.

During this study 62 patients were observed who had clinical manifestations of renal vascular disease, which the authors refer to as diabetic nephropathy.[11] Among the entire study group of 221 cases, not one of the patients who had maintained a satisfactory degree of

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control of diabetes was observed to have manifestations of nephropathy. Only 13 (20 per cent) of the 62 patients with this form of renal disease had made any serious or sustained attempt at control of diabetes.

VALUE OF CONTROL

The above observations attest to the importance of controlled treatment of diabetes in reducing the incidence of complications among young patients with severe diabetes of long duration. These vascular degenerative complications are responsible for more deaths and debility among this group of individuals than are all other causes.[12] Attention to control of diabetes should begin early and aggressive treatment should be maintained continuously from the time the diagnosis is first made.

DISCUSSION

DR. HENRY T. RICKETTS *(Chicago, Ill.)*: The data seem to establish the thesis that good control of diabetes possibly prevents and certainly postpones or minimizes the onset of vascular complications. One should not forget, however, that even with good control a very considerable proportion of young diabetic patients develop vascular lesions after 20 years.

Drs. Wilson, Root and Marble would admit immediately that the control of their best group, although labeled good, was not ideal; and I suspect that if we could obtain ideal control the incidence would be considerably less.

Now the fact that by good control one can at least minimize or postpone these lesions implies that there is something about diabetes which causes them. However, this has been questioned by some investigators on the following grounds—first, that in many instances where control has been admittedly poor for 20 years, vascular lesions are sometimes minimal—not usually, but sometimes; secondly, that in certain cases in which the disease is diagnosed for the first time and is demonstrably mild, vascular lesions are already present.

Now these discrepancies have been explained by variations in constitutional factors, hereditary factors, unknown factors. These explanations are, of course, quite hypothetical. It would be most desirable if one could find a situation in which there was nothing but diabetes operating. Vascular lesions appearing in such an organism would presumably occur without antecedent hereditary or constitutional factors.

This situation is to be found, though perhaps not to our full satisfaction, in the lesions appearing in experimentally produced diabetes in animals. Dr. Lukens, as you are aware, reported some years ago the occurrence of intercapillary glomerulosclerosis in a dog with pituitary diabetes. We do not know what that dog's ancestors were like, but presumably they were in pretty good shape. Also, intercapillary glomerulosclerosis has been reported in diabetic rats by the South American group and one or two others.

In our own work we have found changes in the coronary artery of a dog with alloxan diabetes of three years' duration. The dog, having excreted about 100 Gm. of glucose every day in the urine for a continuous period of 30 months, died when he was 36 months of age. In a coronary artery there could be seen intimal thickening at several points, a rupture of the internal elastic lamina, and invasion of the underlying tissues by phagocytes containing lipids. The rest of the artery was essentially normal and another artery from the same dog was entirely normal, too.

The kidney of another dog with diabetes produced by pancreatectomy showed changes. In this case diabetes was also of 30 months' duration and about 100 Gm. of glucose were lost each day in the urine. The dog died at the age of 36 months. Neither of these dogs, you see, was old. There could be seen very distinctly thickened afferent arterioles in certain glomeruli. Lesions of this type were moderately numerous and were present in perhaps 10 or 15 per cent of the glomeruli.

These are only two cases of experimental diabetes. They do not prove the thesis at all conclusively. The well-controlled diabetic dogs, with diabetes of comparable duration, have not yet died so their tissues cannot be compared. Thus, final judgment will have to be reserved. But this type of observation at least suggests the following conclusion: that diabetes alone in the absence of hereditary or constitutional factors is capable of inducing lesions of blood vessels. It is, of course, improper to state that this is the only factor, or can be the only factor in the human situation, but I can certainly subscribe to the conclusions of Dr. Wilson and his group that, knowing what we do about the effect of poorly controlled diabetes in at least making lesions worse and probably producing them, good control is a goal at which we should all aim.

DR. JOSEPH H. BARACH *(Pittsburgh, Pa.)*: Two important questions face the physician who would treat diabetic patients. The first is, "Can diabetes be controlled?" and the second is "Can the diabetic be controlled?" and, if so, what are the rewards of good control?

I should like to call attention to recent studies dealing with these points. For the sake of better information we divided our patients into two groups: private and dispensary patients. Of these, our experience has been that private patients, constituting a more intelligent group and living on a higher socio-economic level, are and can be more cooperative than dispensary patients.

A survey of diabetic control in 85 diabetics in the private group, including 23,000 urine sugar tests by patients themselves, revealed that 80 per cent of the specimens were sugar free, 8 per cent had only a trace, and 12 per cent of the specimens showed 1.8 per cent or more of sugar. In effect, this means that when patient and doctor cooperate, the patient can be under good control 88 per cent of the time. Considering that a goodly portion of sugar shown in the 12 per cent group occurred in patients who were careless knowingly, it is evident that good diabetic control can be maintained, if the doctor knows what to do and if the patient is properly interested.

In dispensary cases we obtained only 60 per cent of sugar free specimens. The same conditions prevailed for blood sugars. Private cases showed relatively normal blood sugars in 66 per cent, while dispensary patients showed satisfactory blood sugars in only 50 per cent.

These observations, in so far as we are concerned, show that in the diabetic good control can be successfully maintained. That being the case, we come to the second question, "What are the rewards of good control?"

In recent times much has been said about the ocular complications of diabetes that has had an almost rude awakening effect on all of us who treat diabetics. On this point I speak from my own experience only and I wish to say that the story is not as bad as it seemed to be at first sight. In a series of 120 private patients, covering a period of 1 to 27 years, 45 per cent showed diabetic retinopathy and 55 per cent did not. In 156 dispensary cases, also covering a period of 1 to 27 years, 50 per cent showed retinopathy whereas 50 per cent did not. Obviously, the number of patients with diabetes of more than 10 years' duration was considerably smaller than those with less than 10 years. What was more striking was that during the first 5 years of diabetes, dispensary cases showed eye lesions in 34.5 per cent, while private cases showed only 24 per cent. In the 5 to 10 years' period, dispensary cases showed an incidence of 27 per cent of retinopathy while private cases showed only 20 per cent.

At this point, I would like to call attention to the fact that the small red punctate lesions commonly seen in retinae of diabetics are not hemorrhages; they are aneurysmal dilatations of small vessels. They are comparatively seldom seen in nondiabetics. These angiomatous lesions do not bleed, the surrounding area does not show extravasated blood or evidences of absorbed blood. They are fixed, not transient; they do not come and go. They do not have the clinical significance or the prognostic meaning of retinal hemorrhages; or like the flame hemorrhages, the exudates and choroidal lesions of hypertension, nephritis and other disease entities.

In summary, I wish to say that where there is good diabetic control we have found that retinopathies are fewer in number. Our studies show also that the lesions are milder and that they come on later in the disease. All in all there is less blindness.

DR. JAMES LEE WILSON (Closing): We agree that control of diabetes is a matter of relativity. Certainly, among our group of cases with good control, some did not have the perfect results we would like to see. Ideal control is practically nonexistent; but it pays to try to reach that goal as closely as possible.

CASE REPORT

Pituitary Necrosis in a Diabetic During Pregnancy

THE HOUSSAY PHENOMENON IN MAN

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Necrosis of the pituitary is not uncommon. It has frequently been associated with postpartum hemorrhage.[1-5] In 1941 its occurrence in a case of diabetes was reported under the title "The Houssay Phenomenon in Man."[6] Another case of this type is here reported.

CASE HISTORY

A woman aged 27 years was referred as an unstable diabetic on September 22, 1944. One of her maternal grand-aunts had had diabetes at 50 years of age, but otherwise there was nothing significant in the family and personal history. The patient's growth and development had been normal, with no evidence of endocrine imbalance or disturbance. Puberty was uneventful and menstruation was regular thereafter.

She had an operation for the removal of the appendix in April 1943 and during convalescence she had an attack of grippe. Six weeks later there gradually appeared all the cardinal symptoms of diabetes. Sugar tolerance tests made on February 22 and June 6, 1944, were characteristic of diabetes (Table 1). Treatment with diet and protamine zinc insulin was begun.

The control of the diabetes was difficult because of variability and instability of the blood sugar level. At first she was given 12 units of protamine zinc insulin daily, but the dosage was increased and, in 1948, she was using 60 units daily. On September 22, 1944, her weight was 95 pounds. Her diet provided 200 Gm. of carbohydrate, 100 Gm. of protein, and 100 Gm. of fat. She excreted from 50 to 120 Gm. of glucose per day. By August 1948 she had gained in weight up to 114 pounds. She was then on a diet providing 240 Gm. of carbohydrate, 100 Gm. of protein, and 100 Gm. of fat. She was taking 60 units of a fixed mixture of regular insulin and protamine zinc insulin in the proportion of 2 to 1. She excreted from 10 to 30 Gm. of glucose per day.

On August 28, 1948, she married and in November became pregnant. On visits for supervision of her diabetes, it was found that there was excretion of 10 to 12 Gm. of sugar in 24 hours. On a visit made on February 8, 1949, the urine was free from sugar for the 24 hour period. At this time the dosage of insulin was reduced from 60 to 50 units of the mixture per day; the diet was not changed.

On February 14, at 8 a.m., she was seen at her home in typical insulin shock with all the classical signs. She revived when she was given orange juice by mouth. The dosage of insulin mixture was reduced to 40 units.

Read before a meeting of the Clinical Society of the New York Diabetes Association.

TABLE 1. SUGAR TOLERANCE TESTS

	Fasting	After Administration of Glucose			
		½ hr.	1 hr.	2 hrs.	3 hrs.
February 26, 1944					
Blood sugar	130	165	185	245	240
Urinary sugar	Trace	None	0.5%	3.2%	3.1%
June 6, 1944					
Blood sugar	102	175	225	230	194
Urinary sugar	0.1%	0.1%	0.1%	2.8%	1.5%

On February 17, at 9 a.m., she was seen at home again in a typical hypoglycemic shock. At this time she was revived by an intravenous injection of 20 cc. of 50 per cent glucose. In spite of reduction of the insulin dosage to 30 units, hypoglycemic shock occurred again on February 23 and at 9 a.m. she was revived by another intravenous injection of glucose. The insulin was now reduced to 15 units.

On February 24, at 5 p.m., she was found unconscious. It was learned that she had been alone all day, and it was thought that she must have been in this state since breakfast time. She was given the contents of six ampules of 50 per cent glucose solution, each containing 20 cc., but this treatment did not revive her. She was therefore sent to the hospital.

On admission to the hospital on the evening of February 24 she was still unconscious. There was tonic extensor spasm with variable reflexes, but the tendon and abdominal reflexes were absent. The pupils were equal and showed an active response to light. The corneal reflexes were equal and active. There was no nystagmus. The neck was rigid. Kernig's sign was not present. The lungs were clear and resonant throughout. The heart was rapid and regular; there was no murmur and no enlargement; the sounds were of fair quality. The abdomen and extremities were normal except for the reflexes and spasms. The blood count was essentially normal except for a slight leucocytosis. The test of the urine for sugar was positive; the urinalysis was otherwise negative.

She was given solution of glucose intravenously, continuously and at a rapid rate, as shown in Table 2. In spite of this treatment the urine became sugar-free.

TABLE 2. TREATMENT IN HOSPITAL

Date	Time	Urinalysis			Blood Sugar	Glucose Solution (Given Intravenously)		Medication, etc.
		Glucose	Acetone	Albumin		Volume (cc.)	Per cent	
2/24	8:00 p.m.	3+	0	—	—	1,000	10	BP 120/70
	8:30 p.m.	—	—	—	—	50	50	Adrenalin 1:1,000 1 cc.
	9:00 p.m.	2+	0	—	—	50	50	—
	9:30 p.m.	—	—	—	—	50	50	Adrenalin 1:1,000 1 cc.
	10:00 p.m.	—	—	—	—	50	50	Spinal puncture
	11:00 p.m.	—	—	—	—	50	50	Calcium gluconate 15 gr.
	12:00 mid.	1+	0	—	257	50	50	—
2/25	1:00 a.m.	—	—	—	—	—	—	Thiamin chloride 100 mg.
	3:00 a.m.	1+	0	—	—	1,000	10	—
	4:00 a.m.	1+	0	—	—	—	—	—
	6:00 a.m.	—	—	—	—	1,000	5	Thiamin chloride 100 mg.
	8:00 a.m.	1+	0	—	—	50	50	—
	9:00 a.m.	2+	0	—	—	—	—	—
	10:00 a.m.	—	—	—	—	50	50	Thiamin chloride 100 mg. BP 100/60
	12:00 noon	4+	Trace	—	240	—	—	—
	2:00 p.m.	4+	Trace	—	—	1,000	5	Reg. insulin 10 U. subcutaneously
	4:00 p.m.	4+	0	—	—	—	—	—
	7:00 p.m.	3+	0	—	—	1,000	5	—
	9:00 p.m.	4+	0	1+	—	—	—	—
	12:00 mid.	0	0	—	—	—	—	Oxygen
2/26	12:15 a.m.	—	—	—	—	1,000	5	—
	1:00 a.m.	0	0	1+	—	50	50	Adrenalin
	3:00 a.m.	4+	0	2+	—	—	—	Coramine 1 amp. Temp. 105°
	5:00 a.m.	4+	0	2+	—	—	—	Adrenalin Temp. 106°
	7:00 a.m.	4+	0	2+	—	—	—	Atropine 1/150
	9:00 a.m.	—	—	—	—	—	—	Expired

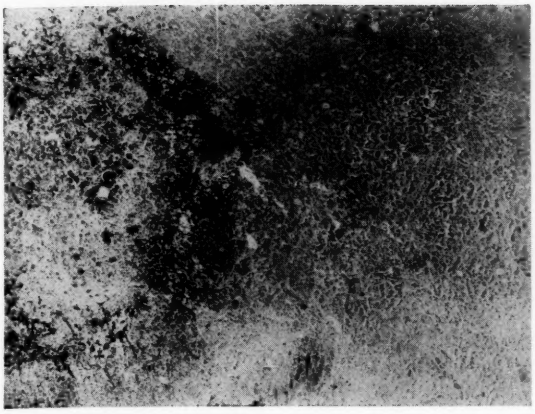

FIGURE 1. Magnification ×35. Intact pituitary cells in right center, surrounded by necrotic tissue. Hemorrhage and degeneration to left of center.

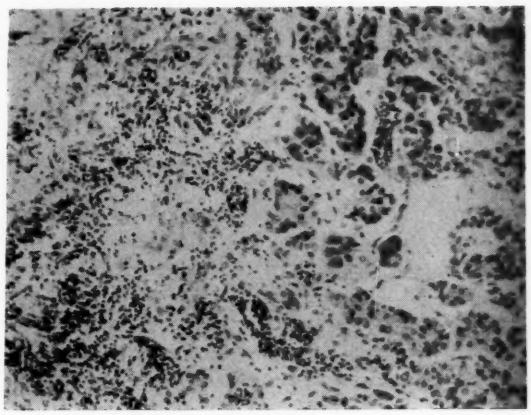

FIGURE 2. Magnification ×250. Same as Figure 1, with higher magnification.

At noon on the following day, her urine contained sugar graded 4 plus, and there was also a trace of acetone. Glycosuria continued; at 2 p.m. she was given 10 units of regular insulin with the infusion of glucose. In response to this treatment with insulin, the urine again became sugar free. More glucose was administered and no acetone was found in the urine.

A spinal puncture was done; the fluid was under normal pressure and clear; it contained 153 mg. of sugar.

In addition to the treatment with injections of glucose, she received calcium gluconate, adrenalin and thiamin chloride. She never regained consciousness. After 36 hours her heart and respiration began to fail. She did not respond to any treatment and expired soon thereafter.

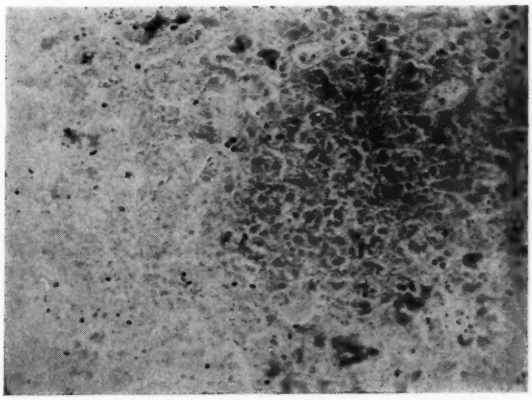

FIGURE 3. Magnification ×250. Typical area of complete necrosis, representing the microscopic appearance of most of the gland. Note indistinct cellular outlines and lack of nuclear detail.

DISCUSSION

While this patient was under observation and treatment, it was the clinical impression that she had suffered from hypoglycemia so long that irreversible changes had occurred in the central nervous system. Therapy had restored hyperglycemia and glycosuria, but because of damage to the brain she had failed to regain consciousness.

In the light of the repeated hypoglycemia, even after reduction of the insulin dosage before she had been admitted to the hospital, the need for such huge doses of glucose intravenously, together with the sharp response to the 10 units of regular insulin given in the hospital at the time that acetone had been found in the urine, the possibility of loss of pituitary function was considered when she died.

POSTMORTEM EXAMINATION

The necropsy was performed by Dr. Chester R. Brown. His most important finding was the striking change in the pituitary. It was approximately twice the normal size. Cut section revealed a mottled yellowish-red color. Microscopic examination showed that a large part of the gland had been destroyed by hemorrhage. (Figs. 1, 2, 3.)

It was also found that there were signs of acute and chronic pericarditis and bronchopneumonia. The pulmonary findings were considered terminal and the pericardial changes were also considered to have no bearing on the course of the final illness.

SUMMARY

A 27-year old diabetic woman in the third month of pregnancy had pituitary necrosis which resulted in intractable hypoglycemia with extreme sensitivity to insulin, and finally death. The changes in the pituitary were demonstrated by necropsy. The condition can be compared to the situation produced experimentally by the animal experiments of Houssay, in which he removed both the pancreas and the pituitary.

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DERMAL REACTIONS TO INSULIN THERAPY

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ABSTRACTS

ALVES, MIGUEL A. MENDES: Sulfonamides and experimental diabetes. Compt. rend. Soc. de biol. *145*:604-06, April 1951.

Prior administration of the sulfonamides is reported to decrease considerably the tolerance for glucose of partially depancreatized animals.

ASHTON, NORMAN *(England):* Retinal micro-aneurysms in the non-diabetic subject. Brit. J. Ophth. *35*:189-212, April 1951 [*Abstr. from* Am. J. Ophth. *34*:1205-06, August 1951].

To ascertain the incidence of retinal microaneurysms in nondiabetics, 336 eyes were examined. When no eye disease was suspected, about 29 per cent of cases had retinal microaneurysms. The lesions were few, limited to the periphery of the field, and often indistinguishable from the diabetic types. In uveitis and diabetes, aneurysm formation is probably explained by the greater vulnerability of the retinal veins to noxious agents. Apart from vascular sclerosis, occasional capillary microaneurysms are the commonest pathological lesions in the retina. These aneurysms are usually small and may be beaded, or they arise from one side of the vessel wall or develop from adhesions of varicose loops. The latter two types are characteristic of diabetes. Aneurysms appear to bear no direct relationship to age or to brachial blood pressure, but are found more commonly in association with chronic diseases of older people and in toxic injuries to the capillaries, particularly on the venous side. Their formation is related to the severity of the suboxidation and subnutrition to which the vascular wall is subjected.

AXELROD, HELEN E.; GULLBERG, MARY GROODY; AND MORGAN, AGNES FAY *(Dept. of Home Economics, Univ. of California, Berkeley):* Carbohydrate metabolism in riboflavin-deficient dogs. Am. J. Physiol. *165*:604-19, June 1951.

Young dogs fed riboflavin-deficient diets of varying composition (high protein, high carbohydrate, or high fat) exhibited declining blood glucose and chloride levels, lowering of carbohydrate tolerance, and the establishment of a state of stress, culminating in dehydration and lowered glucose and chloride circulation, with resulting coma and collapse—conditions simulating those seen in adrenalectomized animals. In the final stage there were indications of sudden and unsuccessful overstimulation of the adrenal glands.

BANCROFT, RICHARD W.; AND DRURY, DOUGLAS R. *(Dept. of Physiology, Univ. of Southern California School of Medicine, Los Angeles):* The glucose equivalent of fed protein. Am. J. Physiol. *166*:213-18, July 1951.

The significance of the G:N ratio of the phlorizinized-depancreatized dog was investigated as an indication of the amount of glucose that is available from protein sources. Particular consideration was given to the amount of glucose that was utilized by the animals under these conditions, as well as to the amounts of sugar and nitrogen that were excreted in the urine. When the urinary G:N ratios were corrected for this utilized glucose and for the nitrogen that may have originated from non-glucose-forming processes, calculated G:N ratios of 5.65 to 5.93 were obtained, instead of the

classical ratio of 3.65. This represents a 90 to 95 per cent conversion of protein to glucose instead of the 58 per cent conversion that has generally been assumed.

BARNS, H. H. FOURACRE; LINDAN, O.; MORGANS, M. E.; REID, E.; AND SWYER, G. I. M. *(Univ. Coll. Hosp., London):* Fetal mortality in pregnant rats treated with anterior-pituitary extracts and in alloxan-diabetic rats. Lancet *2:*841-44, December 23, 1950.

A comparison has been made between the fetal mortality of pregnant rats made diabetic with alloxan and of those given injections of anterior pituitary extract containing the "diabetogenic-growth complex." For the former the stillbirth rate and neonatal death rate were 18 per cent and 19 per cent respectively, although of the liveborn young, only 50 per cent were weaned. When suitable doses of crude anterior pituitary extract were given, however, the stillbirth rate was 100 per cent. It is felt that these results are consistent with the hypothesis that overproduction of the "diabetogenic-growth complex" by the maternal anterior pituitary may be responsible for the high late fetal mortality rate in prediabetic and diabetic women as well as for the subsequent development of diabetes in the former.

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After a survey of the literature, the following conclusions are drawn: Most cases of diabetes mellitus must be regarded as inheritable. The disease probably cannot be considered a genetic entity, because juvenile and senile cases represent different genotypes. Further investigations are needed on series consisting of clear-cut juvenile and senile cases. This genetic difference entails great difficulties in the statistical study of heredity in diabetes, since no sharp line of distinction between the two forms can be found. Therefore, before the problems can be solved, it will be necessary to make genetic studies in which the families are followed until all members have passed the ages at which diabetes may develop.

BAUMGARTNER, M. M. *(Janesville, Wis.):* Office treatment of diabetes mellitus. Wisconsin M. J. *50:*765-69, August 1951.

The ideal treatment provides a maximum of physical fitness with a minimum of inconvenience to the patient. Successful treatment is directly proportional to the patient's understanding of the nature of the disease and how it, as well as its complications, can be controlled or avoided.

BEACH, ELIOT F.; BRADSHAW, PHOEBE J.; AND BLATHERWICK, N. R. *(Biochemical Lab., Metropolitan Life Insurance Company, New York City):* Alloxan diabetes in the albino rat as influenced by sex. Am. J. Physiol. *166:*364-73, August 1951.

The authors report a study of alloxan action after subcutaneous injection into fasted albino rats. In contrast to male rats, females show more susceptibility to the diabetogenic action of alloxan; after developing diabetes, they exhibit polyphagia and frequent acetonuria, whereas males do not increase food consumption and seldom show acetonuria. During the early stages of alloxan action, the female rat develops initial hyperglycemia and the hypoglycemic phase more rapidly than does the male; and the latter phase is generally more severe and prolonged.

A study of oral glucose tolerance shows that severely diabetic rats are frequently able to dispose of considerable amounts of glucose after a brief fast. On fasting twenty-four hours, some of the diabetics develop hypoglycemia, whereas others have normal blood sugar or hyperglycemia. The data suggest that alloxan may produce multiple damage to carbohydrate metabolism and that its effect in curtailing the insulin supply may not be the only factor involved in producing the peculiar diabetic symptoms.

BEATTY, CLARISSA H.; AND WEST, EDWARD S. *(Dept. of Biochemistry, Univ. of Oregon Med. Sch., Portland):* The effect of substances related to the tricarboxylic acid cycle upon ketosis. J. Biol. Chem. *190:*603-10, June 1951.

The administration of various precursors of oxalacetic acid (succinic acid, malic acid, *y*-ketoglutaric acid, aspartic acid, glutamic acid, alanine, *cis*-aconite acid) and oxalacetic acid itself caused a decrease in total urinary ketone-body excretion in rats made ketotic with butyric acid. Inositol also caused a decrease in animals fed butyrate. The tricarboxylic-acid-cycle inhibitors, *trans*-aconitic and malonic acids, caused a decrease in ketonuria; sodium fluoroacetate, also a tricarboxylic-acid-cycle inhibitor, increased urinary ketone-body excretion in rats fed butyric acid. The authors interpreted the anomalous results obtained with malonic and *trans*-aconitic acids

to mean that, in intact animals fed butyrate, the major effect of these acids is not the result of blocking the carboxylic acid cycle.

The results reported are regarded as additional evidence supporting the operation of the tricarboxylic acid cycle in the intact animal and as evidence in vivo for the theory of fatty acid oxidation via the tricarboxylic acid cycle. The data support the theory that ketosis is related to a lack of oxalacetic acid.

BECKER, BERNARD; AND POST, LAWRENCE T. JR. *(Johns Hopkins Univ. and Hosp., Baltimore):* Retinal vein occlusion; clinical and experimental observations. Am. J. Ophth. *34:*677-86, May 1951 [*Abstr. from* Surg., Gynec. & Obst., International Abst. of Surg. *93:*336, October 1951].

In view of the demonstration of aneurysms in the retinal capillaries in diabetic retinopathy, cases of vein occlusion were reviewed. Of 59 eyes adequate for review, 44 had central vein occlusion and 15 had branch occlusion.

In 39 cases of central vein occlusion in which diabetes was excluded, capillary aneurysms were found. The most characteristic defect observed was that of chains of saccular aneurysms on the venous side of the capillary circulation. Hemorrhages and exudates surrounded, and were closely associated with, the microaneurysms.

It is suggested that there is a similarity in the vascular pathology of diabetic retinopathy and central vein occlusion.

BELLET, SAMUEL; AND FINKELSTEIN, DAVID *(Div. of Cardiology, Philadelphia Gen. Hosp. and the Robinette Foundation, Univ. of Pennsylvania):* Significance of QT prolongation in the electrocardiogram: Based on the study of 168 cases. Am. J. M. Sc. *222:*263-78, September 1951.

The authors report a study of 168 patients with QT prolongations (20 per cent or more above normal as calculated by Bazett's formula) in which the etiology was determined from the history, clinical examination, and various studies, including the chemical estimation of electrolytes. Clinical states associated with QT prolongation are classified under the following headings: (1) electrolyte disturbances—diminution of serum Ca and K; (2) myocardial abnormality and/or disease; (3) conditions associated with myocardial anoxia; (4) combined factors, such as hypoglycemia and B_1 deficiency; (5) drugs—quinidine; and (6) unknown etiology. QT segment prolongation, together with characteristic ST and T wave changes, is an important diagnostic criterion of diminution of the serum calcium and potassium, and electrocardiographic guidance is of considerable practical importance in the treatment of these electrolyte deficiencies.

BERGER, G.; AND ZULEGER, F. *(Wien):* Diabetes mellitus and pulmonary tuberculosis in the post-war years. Klin. Med. *6:*66-80, 1951 [*Abstr. from* Excerpta Med. (Int. Med.) *5:*1116-17, August 1951].

From 1945 to 1950, 171 patients with tuberculosis and diabetes were examined (95 men and 76 women); they constituted 5.6 per cent of all cases with metabolic disturbances. Of these 171 patients, the diabetes had been detected first in 110 cases; 40 of these died, 38 from pulmonary tuberculosis. In diabetics, the tuberculosis occurred mainly after the period of famine, frequently in cases of disorders which had previously remained latent.

BLAKLEY, R. L. *(Dept. of Biochemistry, Med. Sch., Univ. of Otago, Dunedin, New Zealand):* The metabolism and antiketogenic effects of sorbitol. Sorbitol dehydrogenase. Biochem. J. *49:*257-71, August 1951.

The oxidation of D-sorbitol in rat-liver slices and homogenates is catalyzed by a dehydrogenase using coenzyme I. The dehydrogenase also oxidizes L-iditol; the specificity of the reaction is discussed. The product of the oxidation of D-sorbitol by the partially purified dehydrogenase is D-fructose. L-iditol is probably oxidized to L-sorbose. The main product of the oxidation of sorbitol by liver slices is glucose. Very small quantities of fructose are also formed. Oxidation of L-iditol by slices produces small amounts of glucose and sorbose. Sorbitol and iditol considerably lower the spontaneous ketogenesis of liver slices from fasted rats. The oxidation of sorbitol by coenzyme I to fructose is reversible; the equilibrium constant is 0.240 ± 0.013. The oxidation of L-iditol to L-sorbitol is also reversible. The optimum conditions for the oxidation of sorbitol by the liver dehydrogenase are pH 7.9-8.1 and 38-40°. $K_m = 7 \times 10^{-4}$ M. Sorbitol dehydrogenase is found in the rat only in liver and kidney. It appears to be widely distributed in mammalian liver.

BLOOM, WALTER LYON; NICHOLS, CAROLINE JEAN; AND BUSEY, JOHN *(Dept. of Biochemistry and Med., Emory Univ. Sch. of Med., Emory Univ., Ga., and Res. Div., Lawson Veterans Admin. Hosp., Chamblee, Ga.):* Intravenous injection of glycogen. Am. J. Physiol. *165:* 288-92, May 1951.

Intravenous injection of glycogen was followed by a rapid rise and fall in plasma glycogen. This polysaccharide was found in the plasma as long as three hours after injection, and elevation of blood reducing substances followed the glycogen administration. The total carbohydrate concentration of plasma exceeded the sum of the glycogen and the reducing concentrations which indicated the presence of intermediate carbohydrate fractions. These fractions tended to parallel the plasma glycogen level. No untoward reactions resulted from intravenous glycogen injections, and hematocrit determinations demonstrated hemodilution as a result of the osmotic activity of glycogen.

BORNSTEIN, J.; AND TREWHELLA, P. *(King's Coll. Hosp., London):* An anti-insulin factor in the plasma of some cases of diabetes mellitus. J. Endocrinol. *7:*33-34, August 1951.

Previous work (by Bornstein) showed that the alloxan-diabetic, hypophysectomized, adrenalectomized (ADHA) rat could be used for the assay of insulin in the plasma of human beings. It appeared that if any factor influencing or modifying the action of insulin were present in the circulation, its demonstration in such a preparation might be possible since no other internal secretions known to modify the action of insulin are acting. Accordingly, the following procedure was adopted: (a) The depression in blood sugar produced by 0.0002 unit of crystalline insulin in each of a group of eight ADHA rats was determined. (b) Four days later, 0.5 ml. of fresh citrated plasma obtained from an untreated case of diabetes mellitus was injected into each of the rats and any alteration in blood sugar determined; thus the plasma insulin level was assayed. (c) Four days later, the reaction to 0.0002 unit of insulin was determined and repeated in a further four days' time. Results showed, first, that eight of the untreated cases and both cases of insulin-resistant diabetes had no "free" insulin present in the plasma and, second, that the remaining untreated cases and the four stabilized patients had insulin concentrations in the normal range previously determined (Bornstein). It was found that, when plasma containing no free insulin as determined by the assay was injected into ADHA rats, resistance to 0.0002 unit of insulin was produced in these animals. This resistance lasted up to six weeks when normal sensitivity was restored. The resistance to insulin was checked in some of the groups of ADHA rats by determining the capacity of the isolated diaphragm to lay down glycogen under the influence of insulin. Results in all cases showed that little or no glycogen was laid down. It has been previously shown that plasma from such patients does not directly inactivate insulin added to it.

BOSSHARDT, DAVID K.; CIERESKO, LEON S.; AND BARNES, RICHARD H. *(Dept. of Biochemistry, Med. Res. Div., Sharp and Dohme, Inc., Glenolden, Pa.):* Preparation of a pancreas derivative having lipotropic activity. Am. J. Physiol. *166:*433-35, August 1951.

The authors describe the method of preparation of a pancreas fraction possessing lipotropic activity which is effective in the prevention of fatty livers in depancreatized dogs maintained with insulin but which is ineffective in preventing the nutritional fatty liver resulting from the feeding of a high-fat, low-protein, and choline-free diet. The lipotropic activity of this material cannot be accounted for on the basis of its choline, methionine, or inositol content or on the basis of free endopeptidases, such as trypsin.

BOWEN, FREDERICK H. *(Jacksonville, Fla.):* The determination of the blood amylase in fluid aspirated from the flank in pancreatitis. South. M. J. *44:*775-77, September 1951.

A new diagnostic aid in acute hemorrhagic pancreatitis is described—the determination of the blood amylase on fluid aspirated from the discolored flank.

BOWEN, T. J. *(Depts. of Biochemistry and Medicine, Univ. of Leeds):* An electrophoretic estimation of the correlation between the cholesterol content and the material extractable from β-globulin in normal and diabetic sera. Brit. J. Exper. Path. *32:*70-76, April 1951.

Diabetic and normal serums have been electrophoretically analyzed. A correlation coefficient has been deduced between total cholesterol levels and material extractable from the serum by the Hardy-Gardiner method, expressed by the reduction in area of the β-globulin peak on the electrophoretic schlieren pattern. No significant

difference was found between the serum of normal individuals and that of well-controlled diabetic patients in that respect. The effect of lipid extraction on the serums as indicated by the electrophoretic analyses was the marked reduction in area of the β-peak, an increase in area of the a_2-globulin peak, and no detectable effect on the a_1- and γ-globulin peaks.

BRADA, ZBYNEK *(Univ. of Berne):* The mechanism of alloxan action. II. On the glutathione economy in the organism following injection of alloxan. Arch. Internat. pharmacodyn. *85:*497-500, February 1951.

The author and his associates demonstrate that reduced glutathione shows considerable fluctuations in the liver, pancreas, and adrenal glands; however, no significant changes were found in kidneys, stomach and heart muscles, spleen, and brain. Whether these fluctuations are really the first step in the pathologic processes leading to alloxan diabetes is yet to be determined.

BRESGEN, C.; AND HEINLEIN, H. *(St. Joseph's Hosp., Coblenz, Germany):* About a new possibility of percutaneous and rectal insulin application and absorption: Preliminary report. Münch. Med. Wchnschr. *93:*657-60, March 30, 1951.

The authors rubbed insulin mixed with hyaluronidase into the breast and abdominal skin (previously cleaned with ether) of diabetics, and through continuous analyses found that the blood sugar was considerably reduced. They also administered this insulin-hyaluronidase mixture rectally and found that the effect on the blood sugar was even more impressive.

BUNTING, JOHN JAMES *(Houston, Texas):* Diabetic dorsal sclerosis of the spinal cord. Dis. Nerv. System *12:*245-47, August 1951.

Two cases of involvement of the posterior columns of the spinal cord in uncontrolled diabetics are discussed. No other etiological factor except diabetes was found. At the time of the report, response to therapy was gratifying. Treatment consisted in better control of the diabetic state, parenterally administered multivitamins, and liver extract in large doses. A plea is made to direct more attention to the nervous system in all diabetics; in this way, neuropathies may be detected in the early phase, when therapy may be more beneficial.

CARR, T. LYLE *(Dept. of Int. Med., Coll. of Med., State Univ. of Iowa, Iowa City):* Problems in the management of diabetes mellitus. J. Iowa M. Soc. *41:*388-92, September 1951.

The author discusses the problems encountered in the management of diabetes mellitus and presents data observed during a twelve-month period—from March 1, 1950, to March 1, 1951—on a total of 244 men and women with diabetes mellitus admitted to a hospital service (other than medical service). These referrals were often necessitated by unrelated disease, acute complications, or chronic degenerations associated with diabetes. There were patients of all ages from early childhood, but more than half were past sixty years. Almost half had evidence of vascular insufficiency in the legs and feet; 20 per cent had gangrene of a portion of the toes, feet, and legs; amputations were carried out during this one-year period on 42, or 17 per cent, of the group studied.

The diagnosis of vascular insufficiency, types of arteriosclerosis, factors influencing arteriosclerosis, therapy of atherosclerosis, and local care of the legs and feet are also considered. It is pointed out that good diabetic control should include measures to keep the blood fat content in the normal range. Good diabetic control, weight reduction and control when indicated, and good local care of the feet should be continuously practiced in an attempt to reduce the incidence of incapacity and amputations among the diabetic population.

CHUTE, A. L.; ORR, J. L.; O'BRIEN, M. J.; AND JONES, E. E. *(Hosp. for Sick Children and the Dept. of Pediatrics, Univ. of Toronto):* Vascular lesions in alloxan diabetic rats. A.M.A. Arch. Path. *52:*105-14, August 1951.

In alloxanized diabetic rats fed a standard diet (55 per cent carbohydrate), vascular lesions failed to develop during the period of observation. This was also true when the diets were altered to contain 36 per cent fat, 40 per cent protein, or 2 per cent cholesterol. In alloxanized diabetic rats fed a standard diet modified to contain 10 per cent sodium chloride (by weight), severe vascular lesions resembling periarteritis nodosa developed frequently (33 to 80 per cent). A 5 per cent sodium chloride diet produced similar lesions more slowly and of a less severe nature. In alloxanized animals that failed to become diabetic, vascular lesions developed when the diet was modified to contain 10 per cent sodium chloride. Although only a small num-

ber of animals were used, a 40 per cent protein, 10 per cent sodium chloride diet failed to produce a significant increase in the number of lesions. The 2 per cent cholesterol, 10 per cent sodium chloride diet gave rise to a high incidence (77 per cent) of periarteritic-like lesions, but no atheroma was seen. Depancreatised diabetic animals and animals made diabetic by the injection of alloxan while the renal vessels were occluded failed to present vascular lesions. It is concluded that the vascular lesions are produced by the action of sodium chloride in those cases in which the kidneys have been damaged by alloxan.

CLOWES, GEORGE H. A. JR.; AND MACPHERSON, L. B. *(Banting and Best Dept. of Med. Res., Univ. of Toronto):* Production of fatty livers by ligation of the pancreatic ducts in rats. Am. J. Physiol. *165:*628-38, June 1951.

Successful ligation of the pancreatic ducts in rats has been accomplished with development of acinar degeneration in 58 per cent of the operated animals and without any signs of abnormality in the islet tissue during the period of observation. Fatty livers develop within a month in animals with acinar degeneration when they are fed a diet free of choline but adequate in protein. A significant decrease in intestinal proteolytic activity, nitrogen absorption, and fat absorption was observed in rats with acinar degeneration. Weight gain following recovery from the operation was typically much reduced below normal in rats successfully ligated. When a pancreatic factor containing proteolytic enzymes is fed to rats with acinar atrophy, it is capable of restoring normal growth and nitrogen absorption and of preventing the development of fatty livers. These findings add further support to the concept that one of the functions of the external pancreatic secretion is to release lipotropic substances, precursors of choline, from the protein in the diet.

COHN, CLARENCE; KATZ, BERTRAM; AND KOLINSKY, MURIEL *(Dept. of Biochemistry, Med. Res. Inst., Michael Reese Hosp., Chicago):* Renal gluconeogenesis in the intact dog. Am. J. Physiol. *165:*423-28, May 1951.

The kidneys of intact dogs, as well as the liver, serve as a source of blood sugar. The rate of glucose production at normal blood-sugar levels approximates 60 mg. per Kg. per hour, about one-fourth of the peripheral glucose requirement. Hyperglycemia is associated with an increase in the rate of gluconeogenesis by the kidney.

COLWELL, ARTHUR R. *(Dept. of Med., Northwestern Univ. Med. Sch., Chicago):* Diagnosis and treatment of diabetic acidosis. West Virginia M. J. *47:*347-52, November 1951.

Diabetic coma due to acidosis is a late manifestation, with distinctive findings preceding and accompanying it. Other forms of coma in diabetic patients must be distinguished from diabetic coma so that treatment may not be misdirected.

COLWELL, ARTHUR R. *(Dept. of Med., Northwestern Univ. Med. Sch., Chicago):* Surgical complications of diabetes mellitus. West Virginia M. J. *47:*351-56, November 1951.

When discriminating methods of managing diabetes are employed intelligently, surgery is as safe for diabetics as for others, provided no vascular disease exists in an advanced form.

CZEBRINSKI, EDWARD W.; AND KARL, MICHAEL M. *(St. Louis):* Pneumaturia in diabetes mellitus. J. Missouri M. A. *48:*715-16, September 1951.

A report is given on a diabetic who had pneumaturia associated with bladder infection due to *A. aerogenes.* The pneumaturia was eliminated after *A. aerogenes* had been cleared by means of streptomycin. This is the fourth case of this type reported in the American literature.

DAVIDSON, SIDNEY *(Lake Worth, Fla.):* Endocrine relations in diabetes mellitus and carbohydrate metabolism. J. Florida M. A. *38:*167-70, September 1951.

Although diabetes is due primarily to a disturbance in carbohydrate metabolism which has its genesis in a pancreatic insufficiency, disturbances of the other endocrine glands may modify the diabetic state both experimentally and clinically. In the usual clinical diabetes, however, there is no evidence that any endocrine gland other than the pancreas is involved.

DE OYA J. C.; GRANDE F.; AND DIAZ, C. JIMENEZ *(Dept. of Physiology, Univ. of Madrid, Spain):* Researches on the mechanism of the effects of clamping the renal pedicle on alloxan diabetes. Bull. Inst. Med. Res. *4:*97-103, April-June 1951.

The inhibitory effect on alloxan diabetes caused by clamping the renal pedicle is not prevented by the administration of dibenamine. This is additional proof that the action is not due to a reflex effect on pancreatic blood supply. Furthermore, the effect is not due to a reflex release of epinephrine, since epinephrine does not give rise to pancreatic vasoconstriction and the effect still continues in the dog treated with dibenamine. In these instances, the release of epinephrine is not admissible. The fact that epinephrine prevents the diabetogenic action of alloxan (even in the dibenaminized dog) presents new problems on its mechanism of action.

DRURY, DOUGLAS R.; AND WICK, ARNE N. *(Scripps Metabolic Clin., La Jolla, and the Univ. of Southern California, Los Angeles):* Insulin and the volume of distribution of glucose. Am. J. Physiol. *166:*159-64, July 1951.

Making use of the methods which measure the dilution of tagged glucose in the body, the authors have determined the effect of insulin on the volume of distribution of glucose in eviscerated rabbits. They find that this volume is not increased above that shown by eviscerated animals not given glucose.

If the amount of intracellular glucose is increased by insulin, this cannot be diffusible out of the cell. It is unlikely that anything more than small amounts of glucose exists in the intracellular compartment.

If insulin increases the permeability of the cell for glucose, there cannot be any increase in the amount of this compound intracellularly as a result of insulin action; glucose diffusing into the cell would have to be changed to some other form almost immediately on entrance.

DRURY, DOUGLAS R.; WICK, ARNE N.; AND MACKAY, EATON M. *(Scripps Metabolic Clin., La Jolla, Cal., and Dept. of Physiol., Univ. of Southern California, Los Angeles):* Effect of insulin on glucose metabolism. Am. J. Med. *10:*763-64, June 1951.

The metabolism of glucose was studied with the aid of C^{14}-labeled molecules. The extrahepatic tissues were found to oxidize glucose to carbon dioxide to a limited extent without the intermediation of insulin. Insulin increased greatly the oxidation of glucose by these tissues, but this effect took several hours to develop fully. During this time, large amounts of glucose disappeared from the blood stream. Since much of the radioactive carbon was found in the blood and body fluids, the authors concluded that a large number of intermediate compounds were formed as a result of insulin action. The chemical nature of these compounds is being studied.

EDITORIAL *(Sydney):* Detection of the unrecognized diabetic. M. J. Australia *1:*769-70, May 26, 1951.

The Diabetes Detection Drive started by the American Diabetes Association in December, 1948, is now fairly well known. Just who in Australia might follow suit is a matter for thought. Public health authorities, whether or not they are interested in diabetes, may not feel that a drive along the American lines is in their province at present. The organized medical profession can accept the responsibility and fulfill it very well. Perhaps the idea is one that the Federal Council of the British Medical Association in Australia might care to refer to the branches for consideration.

EDITORIAL *(Sydney):* Diabetic renal disease. M. J. Australia *1:*772-73, May 26, 1951.

C. J. Bjerkelund, in a recent article on diabetic renal disease, writes that it seems increasingly probable that the so-called vascular complications of diabetes are in fact not complications but part of the disease process itself. In his general discussion, Bjerkelund states that it is now well known that the degenerative vascular changes in diabetes involve in the most serious cases not only the arteries and the arterioles but also the capillaries and veins. To indicate the urgent need for research in the investigation of diabetes and also of arteriosclerosis, Bjerkelund refers to the treatment of diabetes and how it may be so arranged that retinopathy and renal disease can be avoided, pointing out that there is no general conformity of opinion on the matter. In his series, the control of patients has not been sufficiently regular and uniform to permit any conclusions to be drawn. Perusal of the literature does not reveal and general agreement on the matter.

EDITORIAL *(London):* Endocrine control of carbohydrate metabolism. Lancet *2:*106-07, July 21, 1951.

At a meeting of the Diabetic Association in London on July 6, under the chairmanship of Dr. Russell Fraser,

the Banting Memorial Lecture was delivered by Prof. C. N. H. Long. His conclusions were that insulin determines glucose utilization and that the blood glucose level controls insulin production. The maintenance of a steady fasting blood sugar is under more complex control, which depends on adrenalin, ACTH, and the suppression of carbohydrate utilization by the tissues, aided by growth hormone or another anterior pituitary factor.

EDITORIAL *(England):* "Free diet" in diabetes. Brit. M. J. *1:*1133, May 19, 1951.

The report of Dr. C. C. Forsyth, Dr. T. W. G. Kinnear, and Professor D. M. Dunlop on 50 cases of diabetes treated for a period of five years on so-called "free diet" and insulin is of interest and importance to all who treat diabetes. The term "free diet" has been somewhat modified to mean a diet dictated by appetite except for the omission of table sugar, jam, chocolate, and sweets (rather surprisingly, it never contained less than 200 Gm. of carbohydrate per day). The results were very much what might be expected: Clinical control—that is, freedom from hunger, thirst, pruritus, nocturia and ketosis—was readily achieved in 39 out of the 50 cases, the remaining 11 having to be put back on a more conventional restricted diet because of frequent hypoglycemia, excessive insulin requirement, or pruritus vulvae. There can be no doubt that the premature adoption of "free diets" might do great harm and that only after an interval of ten or more years might the harm done become apparent as an increase in the already deplorable incidence of vascular and retinal complications. Meanwhile, until more is known on this subject, those who treat diabetes should not be deterred from continuing reasonably to strive for a physiological ideal, however unattainable it may be.

EDITORIAL *(London):* Mumps and diabetes. Lancet 2:28, July 7, 1951.

In connection with the Survey of Sickness, 43,041 people were asked whether they had diabetes and whether they had ever suffered from mumps. The results revealed no evidence of association between diabetes in adults and a history of mumps. The investigation also indicated that perhaps a quarter of the boys and a third of the girls had mumps by the age of fifteen, and that about a third of the men and half of the women have mumps at some time during their lives.

EDITORIAL *(London):* N. P. H. insulin. Lancet *2:*256, August 11, 1951.

The properties, indications and uses, and advantages of NPH insulin are briefly noted.

FABER, MOGENS; AND LUND, FLEMMING *(Copenhagen County Hosp. Med. Dept. F and the Finsen Lab., Copenhagen):* The human aorta. IV. The aorta in diabetes mellitus. A. M. A. Arch. Path. *52:*239-43, September 1951.

The dry weight, the total cholesterol, and the total calcium were determined in the intima and the media of the aortas of 32 diabetic persons; of these 4 had normal blood pressure and 28 hypertension.

When the figures were compared with those for nondiabetic normotensive and hypertensive persons, it was found that the aortas of the diabetic groups quantitatively followed those of the nondiabetic group. This indicates that the diabetic state is without influence on the arteriosclerosis of the aorta and that the determining factors are age and blood pressure.

FEINBLATT, THEODORE M.; AND FERGUSON, EDGAR A. *(Brooklyn):* Variability of insulin response. Southwestern Med. *32:*308-09, September 1951.

There is a strong central tendency in the normal distribution curve of response to insulin. This means that results of insulin dose can be predicted with a fair degree of reliability. For the standard human of 70 kilograms (150 pounds), each unit of soluble insulin lowers the blood sugar 1.4 milligrams. Forty units would therefore produce shock levels. The statistical analysis is in accord with clinical experience.

FORSYTH, C. C.; KINNEAR, T. W. G.; AND DUNLOP, D. M. *(Dept. of Therapeutics, Univ. of Edinburgh, and Clin. Lab., Royal Infirmary, Edinburgh):* Diet in diabetes. Brit. M. J. *1:*1095-1101, May 19, 1951.

An investigation of the use of a "free" diet in the treatment of 50 diabetics over a period of five years is described. For comparison, 40 dietetically controlled patients were observed over the same period. Clinical control, as defined in the paper, was achieved in 39 of the 50 patients. Although hyperglycemia and glycosuria were the rule, carbohydrate utilization was satisfactory. The incidence of pregnancy was high, and the growth

of the children was unusually rapid. Results were uniformly good in patients over the age of 35, but the insulin requirement of the younger patients tended to rise. Five children and 2 young adults showed a progressive worsening of their diabetic state and had to be given controlled diets for this reason. The change was also necessary for 2 patients who suffered from frequent insulin reactions and for 2 others who became obese and developed pruritus. Only those patients who gave a history of obesity before the onset of diabetes became overweight while taking a "free" diet. The relationship of hyperglycemia to the pathological physiology of diabetes and to the development of degenerative vascular complications is discussed. Although there is no evidence that "exogenous" hyperglycemia is the cause of degenerative complications, there is reason to believe that the high-calorie diets with which it is associated may be responsible for increasing the severity of the diabetic state in children and young adults.

FULLER, C. B. S. *(England):* Case of coma associated with ketonuria in a young adult. Brit. M. J. *2:*652, September 15, 1951.

The author reports the case of a young male adult who was admitted to the hospital as an emergency, in a state of semi-coma. The signs and symptoms resembled those of diabetic acidosis. His urine was strongly positive for acetone and diacetic acid, but no albumin or sugar was found. The blood sugar on admission was 90 mg. per 100 ml. When the history could be obtained, it was discovered that the patient had partaken of an extremely fatty meal three days before admission, and his symptoms began approximately 36 hours after the fatty meal. The author presumed that this large amount of fat, to which the patient was unaccustomed, produced the ketosis. The patient stated that he had suffered from episodes of acidosis as a small boy.

GAGE, MIMS; AND GILLESPIE, GEORGE *(Dept. of Surgery, Ochsner Clin., and Tulane Univ. of Louisiana, Sch. of Med., New Orleans):* Acute pancreatitis and its treatment. South. M. J. *44:*769-75, September 1951.

The authors discuss the etiology, mechanism of production, and symptomatology of acute pancreatitis and the rationale for its conservative therapy by bilateral splanchnic block, intravenous calcium gluconate administration, gastrointestinal drainage, and intravenous infusions of glucose, saline, and blood.

GEIRINGER, ERICH *(Gerontological Res. Unit, Univ. of Edinburgh):* Intimal vascularization and atherosclerosis. J. Path. & Bact. *68:*201-11, April 1951.

The study of 300 aortas and 100 coronary arteries lead to the following conclusions: The normal arterial intima is an avascular structure. It acquires a secondary blood supply if it grows beyond a certain critical thickness. This critical thickness, which varies with each artery, is about 0.5 mm. in the aorta and 0.35 mm. in the proximal part of the anterior descending branch of the left coronary. Intimal vascularization occurs either through an extension of the adventitial plexus into and through the media or by retention of the vascular network of organizing mural thrombi. When both processes occur in the same vessel, anastomoses usually form. This adventitial blood supply of the intima is liable to interference, and most of the clinical effects of atherosclerosis can be traced to the resulting ischemic necrosis of the intima. These phenomena can be appreciated and studied in uninjected routine sections.

GIARDINI, A.; AND ROBERTS, J. *(England):* Concentration of glucose and total chloride in tears. Brit. J. Ophth. *34:*737-43, December 1950 [*Abstr. from* Am. J. Ophth. *34:*1196, August 1951].

The concentration of glucose and chloride at progressive steps of lacrimation is reported. The true glucose of tears averaged 41 per cent of the total reducing substances, compared with 81 per cent concentration in the same subject's blood.

GOLDBERG, R. C.; AND CHAIKOFF, I. L. *(Div. of Physiol., Univ. of California Sch. of Med., Berkeley):* Selective pancreatic acinar destruction by *dl*-ethionine. A.M.A. Arch. Path. *52:*230-38, September 1951.

The authors report on the use of ethionine, a toxic substance, the administration of which leads to the destruction of pancreatic acinous tissue without structural alteration of the encompassed islands of Langerhans. The genesis of the pancreatic lesion induced by ethionine and its effects on other organs are described.

The effect of the administration of *dl*-ethionine was studied in rats from as early as four hours after a single intraperitoneal injection of 50 mg. to as late as 25 days after chronic administrations of 50 mg. daily. Pathological alterations were observed in the acinous portion of the pancreas, the liver, the kidney, and the adrenal glands. Zymogen degranulation and a loss of basal basophilia

in the acinous portion of the pancreas were observed as early as eight to twelve hours after the first injection. In three to five days, inflammation, edema, necrosis, and fibroblastic activity were evident. Marked fibrosis was evident when two to three weeks had elapsed. The pancreatic ducts were unaffected. No cytological changes were observed in the islands of Langerhans at any interval. No evidence of diabetes was detected. An increase in histologically demonstrable fat was observed in the liver as early as eight hours after a single injection. The liver became intensely fatty in 24 hours after a single injection. Within one week the lipid content of the liver had returned to normal despite continued injections of ethionine.

GOLDNER, MARTIN G. *(Brooklyn):* Diabetic coma: Problems of fluid and electrolyte balance. Am. J. Digest. Dis. *18:*235-40, August 1951.

The need for large doses of insulin, for fluid replacement, and for judicious use of glucose is emphasized.

GRAFE, E. *(Würzburg):* The present conceptions of the pathogenesis of human diabetes mellitus. Münch. med. Wchnschr. *93:*1639-52, August 17, 1951.

The author briefly mentions the incidence and course of diabetes mellitus in West Germany during the war and postwar years and refers to the observations of authorities in other countries, discussing past and present concepts of the pathogenesis of diabetes.

GREEN, H. N.; HOPEWELL, J. D.; AND THRELFALL, C. J. *(Dept. of Pathology, Univ. of Sheffield, Sheffield, England):* Plasma pentose levels in pre-eclampsia and their significance. Brit. M. J. *2:*571-74, September 8, 1951.

The authors found a statistically significant rise in the average pentose and phosphorylated pentose content of the blood plasma in a group of women with pre-eclampsia. The degree of the rise showed a correlation with the severity of the clinical condition, reaching a peak in frank eclampsia. It had no individual but only a group significance. It is shown that this rise is probably due to relative uteroplacental ischemia in the pregnant uterus. The authors feel that both direct and indirect evidence supports the hypothesis that this is the proximate cause of pre-eclampsia.

GREENLEE, RALPH G. *(Dept. of Med. of the Scott and White Clin., Temple, Texas):* The treatment of diabetes mellitus today. Southwestern Med. *32:*302-07, September 1951.

A review has been made of the general management of diabetes mellitus, emphasis being placed upon the principles of diet, insulin, exercise, and education. An attempt has been made to individualize the criteria for diabetic control rather than to set a general goal for all types of diabetic patients.

GREIF, STEFAN; AND MORO, E.: Resection hypoglycemia. Münch. med. Wchnschr. *93:*1161-64, June 8, 1951.

Reports are given on two cases of severe spontaneous hypoglycemia following gastric surgery. Resection hypoglycemia is said to be a transitory disorder of carbohydrate regulation.

GROFF, A. E.; ENGELHARDT, H. T.; AND SKELTON, J. M. *(Baylor Univ. Coll. of Med., Houston):* Clinical evaluation of NPH-50 insulin in the management of diabetes mellitus. Texas State J. Med. *47:*547-51, August 1951.

The authors conclude that the data presented indicate that NPH 50 insulin has a definite place in the management of severe or "unstable" diabetes.

GRUNERT, R. R.; MEYER, J. H.; AND PHILLIPS, P. H. *(Dept. of Biochemistry, Coll. of Agriculture, Univ. of Wisconsin, Madison):* Effect of dietary electrolyte deficiencies on the blood and liver levels of reduced glutathione. Am. J. Physiol. *165:*568-73, June 1951.

The authors investigated the effect of dietary electrolyte deficiencies on the blood and liver glutathione levels in rats, with the following results: (1) A sodium deficiency was not unique in lowering the level of blood glutathione. (2) The blood glutathione level was lowered in potassium, chloride, sodium-potassium, and sodium-chloride-deficient rats. (3) In contrast, the blood glutathione of sodium-deficient chicks and pigs was unaffected. (4) Liver glutathione remained normal in the electrolyte-deficient rats in proportion to body weight. (5) The blood glutathione of rats increased with an increase in age. (6) Desoxycorticosterone acetate temporarily reversed the effect of the sodium deficiency.

GRUNERT, R. R.; AND PHILLIPS, P. H. *(Dept. of Biochemistry, Coll. of Agriculture, Univ. of Wisconsin, Madison):* Effect of stress and the adrenocorticotrophic hormone on blood glutathione. Am. J. Physiol. *165:*574-79, June 1951.

The effect of stress, the adrenocorticotrophic hormone, and desoxycorticosterone acetate on the blood, liver, and kidney glutathione of the rat has been studied with the following results: (1) Cold, histamine and epinephrine, single and repeated injections of ACTH, and repeated injections of DCA had no effect on the blood glutathione level. (2) Repeated injections of ACTH and DCA had no effect on the glutathione content of the liver or kidney. (3) The results have been offered as evidence against the hypothesis that the pituitary-adrenal system is involved in the mechanism for the decreased level of blood glutathione found in electrolyte-deficient rats.

HAANES, MARY LOU; AND GYORGY, PAUL *(Nutritional Service, Dept. of Pediatrics and Gastrointestinal Section, Dept. of Med., Univ. of Pennsylvania, Philadelphia):* In vitro action of a new lipotropic fraction in the pancreas. Am. J. Physiol. *166:*441-50, August 1951.

A highly lipotropic pancreatic fraction (designated A-I), without demonstrable direct proteolytic activity, has been studied in vitro. It has been found to contain an active proteolytic enzyme combined with an excess of an enzyme inhibiter. The enzyme has been tentatively identified as trypsin, and the inhibiter as pancreatic trypsin inhibiter. The action of the inhibiter may be overcome by the addition of a substance present in duodenal juice and presumed to be enterokinase. This action of enterokinase has not been previously noted.

It is assumed that the lipotropic activity of fraction A-1 is based on enzymatic liberation of methionine from ingested protein after the activation of the proteolytic enzyme in the small intestine. The use of a microbiological assay for methionine is described as a method of testing enzyme activity. An arbitrary unit [the (TU) meth] is defined as the micrograms of methionine released per hour per microgram of enzyme.

HINKLE, L. E., JR.; EDWARDS, C. J.; WOLF, S.; KENNEDY, M. A.; PUGH, B. L.; AND CONGER, G. *(Dept. of Med. of the New York Hosp. Cornell Med. Center, New York City):* Studies in diabetes mellitus. II. The occurrence of a diuresis in diabetic persons exposed to stressful life situations, with experimental observations on its relation to the concentration of glucose in blood and urine. J. Clin. Investigation *30:*818-37, August 1951.

In persons with diabetes mellitus, exposure to stressful life situations may lead to a diuresis. This diuresis is characterized by a 200 to 500 per cent increase in the rate of water excretion, accompanied by a rise in the excretion of chlorides and ketone bodies.

The stress diuresis which occurs in aglycosuric diabetic persons is similar to that observed in nondiabetic individuals. When stress diuresis occurs in diabetic persons who are glycosuric, the rate of glucose excretion rises in parallel with the rate of water excretion, and there is no major change in the glucose concentration of urine. Stress diuresis is not dependent upon osmotic changes associated with the excretion of glucose in the urine or upon changes in the concentration of glucose in the blood.

A stress diuresis may lead to a rapid loss of large amounts of water, glucose, and chlorides and may be an important factor in the development of diabetic acidosis and coma. The ingestion of concentrated glucose solutions is well tolerated by diabetic persons in the absence of stress, but in a setting of stress the ingestion of concentrated glucose solutions may accentuate the loss of water and chlorides.

HOUSSAY, BERNARDO A. *(Inst. of Biol. and Exper. Med., Buenos Aires):* Action of sex hormones on experimental diabetes. Brit. M. J. *2:*505-10, September 1, 1951.

After subtotal pancreatectomy, diabetes appears less frequenly in female rats than in males. This sexual difference is due to a provocative action of the testes and a protecting influence of the ovaries. Substances with estrogenic effect decreased the incidence of diabetes in white rats following subtotal pancreatectomy. Androgens, on the contrary, increased it and other steroids had no effect. The mechanism of protection is apparently due chiefly to the action of the ovaries and estrogens in the stimulation of hypertrophy and hyperplasia of the islets of Langerhans, with production of new beta cells at the expense of the centroacinar cells. The peripheral action of estrogens on carbohydrate metabolism is not yet well known. The probability of preventing some forms of experimental diabetes certainly exists.

It is evidently worth while to continue this line of investigation, using prolonged administration of the substances already studied and other new ones, either alone or combined with insulin, in order to prevent or treat other types of experimental diabetes and eventually human diabetes. It would be of value to discover substances which have no estrogenic effect but cause

hyperplasia of the islets and inhibit the hypophysis or adrenals. Diabetes can possibly be controlled by other mechanisms, such as direct or indirect action on tissue metabolism.

HOUSSAY, B. A.; LOTT, W. A.; AND MARTINEZ, C. *(Buenos Aires):* Action of certain sulfur substances upon alloxan diabetes and pancreatic diabetes. Compt. rend. Soc. de biol. *145:*591-92, April 1951.

The oral administration of two new organic compounds containing sulfur produced (a) protection against the diabetogenic and toxic action of alloxan, (b) decrease in frequency of occurrence of diabetes in animals subjected to ablation of 95 per cent of the pancreas, (c) increase of the free sulfhydril content of the liver and of certain tissues.

ILLING, ELIZABETH K. B.; AND GRAY, C. H. *(King's Coll. Hosp., Denmark Hill, London):* Retinal metabolism in diabetes: The metabolism of retinae of normal and alloxan-diabetic rabbits. J. Endocrinol. *7:*242-47, August 1951.

The authors compared the oxidation of pyruvate by normal and diabetic retinas. A lowered metabolism in the alloxan-diabetic retina was observed when glucose was the substrate.

INGLE, DWIGHT J.; AND NEZAMIS, JAMES E. *(Res. Labs. Upjohn Company, Kalamazoo, Mich.):* Effect of antibiotics upon survival of the eviscerate rat. Am. J. Physiol. *166:*349-53, August 1951.

Eviscerate rats were given continuous intravenous injections of glucose and insulin, with and without antibiotic drugs. Penicillin, streptomycin, neomycin, and aureomycin each prolonged survival to a significant extent. Of all of the drugs tested, a mixture of penicillin and streptomycin had the most favorable effect upon survival.

JOHNSON, HERBERT W.; AND RYNERSON, EDWARD H. *(Mayo Clin., Rochester, Minn.):* A diabetic patient on a high fat diet for twenty-nine years without complications. Proc. Staff Meet., Mayo Clin. *26:*329-31, September 29, 1951.

The authors report the case of a 61-year old man who had meticulously followed a diet containing approximately 15 Gm. carbohydrate, 45 Gm. protein, and 150 Gm. fat during his 29 years of diabetes. It is interesting that his blood pressure and the neurologic and ophthalmoscopic findings were normal. All vessels were found to be open and normal to palpation. The urine did not contain albumin, and the values for blood fats were normal. Whether his diet had any part to play in the freedom from complications is, of course, unknown. It is also of interest that there were no signs of any deficiency of vitamins in spite of the fact that all vegetables were boiled three times and the patient followed such a restricted diet.

KENNY, A. J.; CHUTE, A. L.; AND BEST, C. H. *(Toronto):* A study of the prevalence of diabetes in an Ontario community. Canad. M. A. J. *65:*233-41, September 1951.

Samples of blood and urine from 4,419 persons (81 per cent of the town's population) in Newmarket, Ontario, were examined for glucose. All age groups were covered with the exception of the preschool group. Fifty-four diabetics were seen among the 4,419 persons tested, an incidence of 1.2 per cent. Twenty-one of these were previously undiagnosed.

KERSLEY, G. D.; MANDEL, L.; JEFFREY, M. R.; BENE, E.; AND TAYLOR, K. B. *(South-West and Oxford Regional Rheumatism Research Unit, Royal National Hosp. for Rheumatic Diseases, Bath, England):* Hypoglycemia in treatment of rheumatoid arthritis. Brit. M. J. *2:*574-78, September 8, 1951.

Of 72 cases treated by hypoglycemia, 82 per cent were temporarily improved, 44 per cent markedly so. The improved figure had dropped to 58 per cent in two months, but 7 had progressed to complete remission after six months. In a control series without insulin therapy, 78 per cent improved on a similar hospital regimen, but only 14 per cent markedly. A second course of treatment had less effect than the first. Gain in weight was considerable and occurred in all but 3 cases; there was a tendency toward improvement in the sedimentation rate but not in the hemoglobin level. Reduction in circulating eosinophils occurred almost without exception. Observations on changes in potassium and steroid excretion were made. The clinical response to hypoglycemia was compared with subsequent ACTH treatment and was found to correlate closely. The possible mechanism and practical value of hypoglycemia therapy in rheumatoid arthritis are discussed.

KERSLEY, G. D.; MANDEL, L.; TAYLOR, K. B.; AND JEFFREY, M. R. *(South-West and Oxford Regional Rheumatism Research Unit, Royal National Hosp. for Rheumatic Diseases, Bath, England):* Spontaneous hypoglycemia after insulin therapy in rheumatoid arthritis. Brit. M. J. *2:*578-80, September 8, 1951.

Two cases of rheumatoid arthritis developed attacks of spontaneous hypoglycemia in the early morning, shortly after the end of second courses of insulin hypoglycemia therapy. The attacks were controlled by a high-protein diet with a bedtime feeding, and the tendency disappeared within two weeks. When the blood sugar of six other patients was observed for twelve days after insulin administration was dropped, it was found to be at its lowest about the tenth day.

KLOOS, K. *(Germany):* Pathological and anatomical bases for "embryopathia diabetica." Klin. Wchnschr. *29:*557-60, September 1, 1951.

The syndrome designated as "embryopathia diabetica" consists of intra-uterine death of fetus, debility, hydrops congenitus and fetal erythroblastosis without anemia, overgrowth and adiposity of newborn babies, severe conditions of faulty development in the form of idiocy, cretinism, and symptoms resembling "postencephalitis" without any infectious basis in fetuses and newborn babies as well as in small children of diabetic mothers. It is considered mainly the result of maternal hormonal imbalance. The disorder of the carbohydrate economy is a pathogenic factor, but is apparently of secondary nature.

KNOWLES, GEORGE M.; AND KRISTAL, J. J. *(Hackensack, N. J.):* The use of the various insulins: With special reference to timing. J. M. Soc. New Jersey *48:*357-60, August 1951.

The five insulin preparations in use today are described, together with their time activity and their uses. The variable factors that affect the time of action of insulin are mentioned.

KRAMER, LOUIS I.; PRIOR, JAMES H.; BURNS, LOUIS E.; O'REILLY, EDWIN B.; BECK, IRVING A.; RUSSELL, AMY; AND ZAMIL, EDWARD *(Committee on Diabetes, Rhode Island Med. Soc.):* Diabetes. Rhode Island M. J. *34:*391-92, July 1951.

The results of Diabetes Detection Week for 1950 were as follows: The over-all number of urines checked was 5,852; the number of positive urines, 101 (or 1.7 per cent); the number of urines showing 2 to 4 plus, 40; the number showing trace to 1 plus, 61. There were 110 blood sugars reported; 27 were elevated. Of the over-all number of urines checked, the State Laboratory of the Rhode Island Department of Health made 2,850 tests; private physicians, 1,479; private laboratories, 32; industry, 674. It is interesting to note that out of 5,852 urines checked, 3,025 were done on children of high school age; there were 9 positive tests, or 0.2 per cent, in this group.

LEVITAN, BENJAMIN A. *(Duke Univ. Sch. of Med., Durham, N. Car.):* Effect in normal man of hyperglycemia and glycosuria on excretion and reabsorption of phosphate. J. Appl. Physiol. *4:*224-26, September 1951.

In nine normal subjects, the tubular reabsorption of phosphate was depressed by 21 per cent when glucose was given intravenously to measure maximal glucose reabsorption (glucose Tm). The mean phosphate excretion increased by 78 per cent, and the clearance of phosphate increased by 100 per cent.

LOMINACK, REYBURN W. *(Newberry, S. C.):* Observations on the effects of Priodax on blood sugar and nonprotein nitrogen. J. South Carolina M. A. *47:*237, July 1951.

Nine cases were presented to show the effect of Priodax on the blood sugar and N.P.N. These showed an average increase in the blood sugar of 38 mg. and in the N.P.N. of 8. In several of the patients with unusually high blood sugars, determinations were made the following morning and showed normal values.

LOWREY, G. H. *(Univ. of Michigan Med. Sch., Ann Arbor):* Care of the juvenile diabetic. Univ. Michigan M. Bull. *17:*274-81, August 1951.

The care of the juvenile patient with diabetes must be individualized. The educational program of the patient and his parents is of utmost importance in preventing the development of psychological problems which may interfere with effective control of the disease. Diet and insulin are so balanced that the danger of either an insulin reaction or acidosis is minimized and the patient can lead an active and nearly normal life. Instruction of the child and his parents should alert them to the signs and symptoms of possible emergencies and their immediate care. At the same time, emphasis is made on

the relatively minor limitations that the disease will impose upon the patient. He should be taught to respect the disease, but not to fear it.

MACKLER, BRUCE; LICHTENSTEIN, HENRIK; AND GUEST, GEORGE M. *(Children's Hosp. Res. Foundation and Dept. of Pediatrics, Univ. of Cincinnati):* Effects of ammonium chloride acidosis on the action of insulin in dogs. Am. J. Physiol. *166:*191-98, July 1951.

To determine the effects of a nonketogenic type of acidosis on the action of insulin, insulin sensitivity tests were made with six nondiabetic fasted dogs in normal states and in states of severe acidosis induced by slow intravenous perfusion of ammonium chloride.

During the development of acidosis in the fasted animals, concentrations of sugar in the blood tended to rise slightly, with maximal increases around 35 mg. per 100 cc. above the fasting level. Standard doses of insulin administered intravenously in severely acidotic dogs produced less fall in the concentration of blood sugar, with slower rate of fall and slower recovery to initial levels in the three-hour test period, than in the same dogs in nonacidotic states. Levels of plasma potassium and inorganic phosphorus tended to change very little or to remain stationary after injections of insulin in the acidotic dogs, whereas in nonacidotic states, changes in concentration of plasma potassium and inorganic phosphorus (both sharply decreasing and then returning to initial level) paralleled closely the changes of blood sugar induced by insulin.

Conditions of acidosis probably inhibit the action of insulin by interfering with processes of phosphorylation that are involved in the cellular uptake of sugar, potassium, and phosphorus from the plasma.

MCGHEE, EVA C.; PAPAGEORGE, EVANGELINE; BLOOM, WALTER LYON; AND LEWIS, GEORGE T. *(Dept. of Biochemistry, Emory Univ., Ga.):* Effect of hyperinsulinism on brain phospholipide. J. Biol. Chem. *190:*127-32, May 1951.

Massive doses of insulin were administered to 24 rabbits. Twelve were given no further treatment; 6 were given 0.5 Gm. of lecithin one hour after the insulin; and 6 were given sufficient glucose to maintain the blood sugar above a convulsive level in spite of the insulin dosage. Twelve untreated rabbits served as controls. Analyses were made for glucose and lipid phosphorus of whole blood and for lipid phosphorus of whole brain.

Lipid phosphorus of whole blood was not significantly affected by the administration of insulin. However, the insulin treatment produced a consistent and significant decrease in the brain lipid phosphorus of the order of 10 per cent. The decrease was effected in a period of about six hours and was not reversed by the administration of lecithin or glucose.

MEDICAL FORUM, THE *(Chicago):* Doctors put on alert for diabetic nostrum. Wisconsin M. J. *50:*792, August 1951.

The Food and Drug Administration has asked all physicians in the United States to assist the Government in tracking down packages containing Cacalla Composita, Mexican Indian Root mailed to potential patients. It is offered for sale by the Mexican Indian Root Company, Mexico City, under the name of Dr. Miguel C. Martinez, general manager. It is described by the FDA as "worthless and extremely dangerous if employed as a substitute for insulin."

MEYTHALER, F.; AND LOSSL, H.-J. *(Med. Klin. allgemeinen städtischen Hosp., Nürnberg):* Treatment of diabetes mellitus predicated upon the body constitution. Therap. Gegenw. *90:*252-56, July 1951.

The authors believe that diabetic subjects of different constitutions (pyknics, leptosomes, and athletes) react differently and require different kinds of treatment. Direct correlation of the nature of complications and the body structure types has yet to be made, but there are indications that a connection exists.

MILLER, ELDON S. *(Kansas City, Kan.):* Simplified management of diabetes. M. Times, New York *79:*489-96, August 1951.

A concise method is presented by which the physician can treat the diabetic with reasonable accuracy and minimal effort on the part of both the physician and the patient.

MILMAN, ANNE E.; DE MOOR, PIETER; AND LUKENS, F. D. W. *(George S. Cox Med. Res. Lab., Univ. of Pennsylvania, Philadelphia):* Relation of purified growth hormone and insulin in regulation of nitrogen balance. Am. J. Physiol. *166:*354-63, August 1951.

Employing purified growth hormone (Armour), the authors studied the relation of growth hormone and

insulin in the storage of nitrogen in totally depancreatized cats and in hypophysectomized-depancreatized cats, with the following conclusions: 1. Insulin is essential to the protein anabolic effect of growth hormone. 2. An increased secretion of insulin presumably occurs in response to growth hormone in normal animals. 3. This increased demand for insulin may be sufficiently great to exceed the body's functional reserve. This is suggested by the increment in insulin needed to restore normal nitrogen retention, by the production of diabetes, and by the work of others on insulin resistance. 4. Much, if not all, of the diabetogenic action occurs in the tissues and not upon insulin itself (cf. Houssay animals). 5. Although insulin is an essential synergist, the level of growth hormone appears to play a dominant role in the regulation of nitrogen metabolism and to be independent of minor changes in the insulin supply.

MONTENERO, D.; AND ETTORE, F. *(Trieste):* Study on the relationship between diabetes mellitus and tuberculosis. Rassegna giul. med. *6:*284-88, 1950 [*Abstr. from* Excerpta Med. Int. Med. *5:*1116, August 1951].

In 6,629 cases of pulmonary and extrapulmonary tuberculosis, diabetes mellitus occurred in 100 subjects (1.5 per cent). The treatment with antibiotics and insulin markedly improved the prognosis of tuberculosis in diabetes.

NEWMAN, BEN A.; AND FELDMAN, FRED F. *(Cedars of Lebanon and Los Angeles County Gen. Hosp.):* Effects of topical cortisone on chronic discoid lupus erythematosus and necrobiosis lipoidica diabeticorum. J. Invest. Dermat. *17:*3-6, July 1951.

Ten patients with chronic discoid lupus erythematosus and three patients with necrobiosis lipoidica diabeticorum were treated topically with cortisone in an ointment base. Some degree of involution, varying from minimal to almost complete clearing, was noted in all the patients studied.

NORDMAN, LARS OLAV *(Sater, Sweden):* Diabetes and depression. Nord. med. *46:*1411-12, 1951.

In a case of diabetes mellitus complicated by a depressive mental state, probably a depressive phase of a manic-depressive psychosis, electroshock treatment not only produced an improvement in the mental condition but also immediately caused a slight but distinct fall in the blood-sugar level. During the ensuing months the improvement in the diabetes continued. The cause of this effect is discussed, and some previous papers on diabetes and mental diseases are mentioned.

OCCHINO, NICHOLAS R. *(Med. Dept. of the Charles S. Wilson Mem. Hosp., Johnson City, N. Y.):* Manifestations of hypoglycemia in clinical practice. New York State J. Med. *51:*1499-1503, June 15, 1951.

Seven representative case histories are cited to illustrate the capacity of functional hypoglycemia to simulate other disease entities. The various manifestations of hypoglycemia are briefly reviewed in the comments following each case presentation.

OLSON, J. A.; STEFFENSEN, E. H.; SMITH, R. W.; MARGULIS, R. R.; AND WHITNEY, E. L. *(Henry Ford Hosp., Detroit):* Use of adrenocorticotropic hormone and cortisone in ocular disease. A.M.A. Arch. Ophth. *45:*274-300, March 1951 [*Abstr. from* Surg., Gynec. & Obst., International Abst. of Surg., *93:*221, September 1951].

Thirty-seven patients with inflammatory, degenerative, hereditary, and other diseases of the eye were treated with ACTH; 14 others were treated with cortisone. Twenty-two of the patients receiving ACTH showed a reduction in carbohydrate tolerance, but only one of the cortisone-treated patients showed a carbohydrate anomaly.

PALMER, LESTER J. *(Mason Clin., Seattle):* Selecting the appropriate insulin. Clin. Med. *58:*170-72, July 1951.

There will always remain a need for two types of insulin: namely an insulin with prompt and short action and a prolonged-acting insulin. The latter, of necessity, is less prompt in effect. It might be desirable if all insulins except one of each type could be eliminated, thus diminishing at least some of the confusion which exists in professional as well as lay minds at present.

Delayed-action insulin will remain the basic insulin most practical and efficient in controlling the average uncomplicated diabetic patient. Prompt-acting insulin of short duration will remain the desirable preparation for use during emergencies and when acute associated or complicating states make the immediate future not entirely predictable. Undoubtedly, further efforts will

be based upon future studies and experience to evolve an even more satisfactory formula for preparing insulin for use; the improvements to date are reassuring the diabetic and his physician that constant effort in this direction is being made.

PALMER, LESTER J.; FLAHERTY, NEIL F.; CRAMPTON, JOSEPH H.; AND JOHNSON, ROGER H. *(Seattle):* The influence of rutin upon diabetic retinitis. Northwest Med. *50:*669-71, September 1951.

Thirty-six patients with diabetic retinitis were treated with 60 mg. of rutin four times a day for an average of 15 months. After treatment, 11 patients had a retinal picture that was unchanged, 8 showed improvement and 17 were worse. The results were thought to be sufficiently encouraging to warrant further investigation of rutin.

PEASE, J. C.; AND COOKE, A. M. *(Radcliffe Infirmary, Oxford, England):* The family doctor and diabetic coma. Brit. M. J. *2:*336-38, August 11, 1951.

The outcome of 111 cases of diabetic precoma and 74 cases of diabetic coma admitted to the Radcliffe Infirmary between 1932 and 1950 is presented. Suggestions are made for improving the prognosis for diabetic patients with progressive ketosis, and stress is laid on the important part that the family doctor can play in improving the outlook for these patients. Every opportunity should be taken to teach diabetic patients about their disease and how to look after themselves when ill.

PENNOCK, L. LEWIS *(Pittsburgh):* Diet and insulin in diabetes. Pennsylvania M. J. *54:*872-74, September 1951.

A plan is described for a simple diabetic diet.

PERKOFF, GERALD T.; AND TYLER, FRANK H. *(Dept. of Med., Univ. of Utah Coll. of Med., Salt Lake City):* Insulin tolerance tests in patients receiving large doses of exogenous insulin. Am. J. Med. *10:*777, June 1951.

The authors performed intravenous insulin tolerance tests in patients receiving insulin shock therapy for psychoses. Each patient had received excessive doses of insulin five times weekly for several weeks. The results of the insulin tolerance tests in these patients came within the limits of normal. The blood sugar fell to hypoglycemic levels in 30 minutes and returned to control levels or above in one hour. The authors conclude that the insulin sensitivity remained the same in spite of the repeated administration of large doses of insulin.

PERSKY, LESTER; RAVIN, HERBERT A.; JACOB, STANLEY; AND SELIGMAN, ARNOLD M. *(Yamins and Kirstein Labs. for Surgical Res., Beth Israel Hosp., and the Dept. of Surgery, Harvard Med. Sch., Boston):* Serum lipase activity in experimental acute hemorrhagic pancreatitis. Am. J. Physiol. *166:*413-15, August 1951.

Ten mongrel dogs with acute hemorrhagic pancreatitis induced surgically by injection of bile into the major pancreatic duct followed by ligation of the duct uniformly showed elevation in serum lipase activity on the third or fourth postoperative day, ranging from 22 to 45 per cent over preoperative values. The increase in lipase activity of the blood was seen more regularly than in patients. The relatively wide range of serum lipase activity in normal dogs makes it impossible to establish an artibrary serum lipase activity as diagnostic of the presence or absence of pancreatitis.

PETERS, JOHN H. *(Univ. of Pittsburgh Sch. of Med.):* Vascular complications of diabetes. Am. Pract. *2:*669-72, August 1951.

The author reviews the current literature on the complications of diabetes of long duration. The data indicate that, as the duration of diabetes increases, the proportion of patients with vascular disease also increases until, after 20 years, 90 to 100 per cent of all cases show clinically detected stigmata.

PHILLIPS, D. M. P. *(Courtauld Inst. of Biochemistry, Middlesex Hosp. Med. Sch., London):* Further observations on the action of chymotrypsin on insulin. Biochem. J. *49:*506-12, September 1951.

Throughout the digestion of insulin by chymotrypsin, the enzyme remains almost fully active and the digestion rate is unaffected by the presence of urea or the products of the digestion. The pH-digestion rate curve for this proteolysis has two optima, at pH 8.6 and 9.5. The double optimum is not due to inactivation of part of the insulin or the enzyme, and the bonds split at pH 7.6 and 9.9 appear to be the same. Insulin is in-

activated at the same rate at pH 7.6 and 9.9 by chymotrypsin. The degradation has the character of an "all-or-none" reaction as postulated by Tiselius and Eriksson-Quensel. Every molecule degraded has undergone the fission of thirteen or fourteen bonds, irrespective of the number of intact insulin molecules present.

PITESKY, ISADORE; LAST, JULES H.; AND BOND, EPPERSON E. *(Dept. of Pharmacology, Univ. of Illinois Coll. of Med., Chicago):* Approximation of the tubular maximum for reabsorption of glucose using venous blood for plasma glucose levels. Am. J. Physiol. *165:*407-10, May 1951.

Arteriovenous differences of plasma glucose concentrations in the dog under basal conditions are independent of the level of glucose in the arterial blood and of the duration of the hyperglycemia. Tmg values calculated with venous glucose values are significantly lower than those calculated with arterial glucose concentrations. Tmg values calculated from venous glucose values may be used in preliminary experiments, but are not recommended in definitive renal studies.

POST, LAWRENCE T.; AND STICKLE, ARTHUR W. *(St. Louis):* Fundus changes in juvenile diabetics. Am. J. Ophth. *34:*1119-26, August 1951.

In 59 cases studied, the grade of control of diabetes as well as the eye findings and general health became progressively worse the longer the duration of the disease. However, it was evident that the patient who was able to maintain good control showed less pathologic progress than the one whose diabetes was poorly controlled and had a minimal number of degenerative changes resulting from the diabetes.

In juvenile diabetics the control of the diabetes, as well as the duration of the disease, is an important governing factor in the development of retinopathy, kidney damage, and poor general physical condition. The most common degenerative change found in this series of diabetics was in the vascular system of the retina. Capillary aneurysms and small round hemorrhages were the first changes to be seen; these were usually found in the area between the superior and inferior temporal vessels. The very early lesions were visible only on careful examination. In juvenile diabetics, examination of the retina is a fairly reliable method of estimating the condition of the vascular system in general, and the degree of associated renal damage.

RANNEY, R. E.; CHAIKOFF, I. L.; AND DOBSON, E. L. *(Div. of Physiology of the Sch. of Med. and Donner Lab., Univ. of California, Berkeley):* A procedure for functional hepatectomy of the unanesthetized fowl. Am. J. Physiol. *165:*588-95, June 1951.

The authors describe a procedure for the functional hepatectomy of the relatively untraumatized, unanesthetized domestic fowl which consists in tightening two exteriorized ligatures previously placed around the afferent hepatic blood vessels. This reduces the circulation to the ligated liver by about 99 per cent.

RANNEY, R. E.; CHAIKOFF, I. L.; AND ENTENMAN, C. *(Div. of Physiology, Univ. of California Sch. of Med., Berkeley):* Site of formation of plasma phospholipides in the bird. Am. J. Physiol. *165:*596-99, June 1951.

By injecting P^{32} into functionally hepatectomized fowls and determining the recovery of P^{32} in phospholipides of the plasma and of certain tissues, the authors found that the bird's liver is concerned with the formation of plasma phospholipide, that probably significant amounts of plasma phospholipide are formed in an extrahepatic tissue or tissues, and that the small intestine and/or kidney could have served as the site for the formation of the labeled plasma phospholipide, although the possibility of other sites of synthesis have not been excluded by the present study.

REID, E. *(Univ. of Cambridge):* Some studies with diabetogenic pituitary preparations: Growth hormone (GH) and adrenocorticotrophic hormone (ACTH) as diabetogenic agents. J. Endocrinol. *7:*36-37, August 1951.

In routine assays, GH preparations are administered daily to intact cats until 5 Gm. of glucose are excreted. The use of a hyperglycemic (rather than the slower glycosuric) response might save time and material. If, however, a GH preparation is administered repeatedly to a single cat at different dose levels, with induction of hyperglycemia but not glycosuria in each test, a relationship between dose and period of treatment required cannot readily be discerned because of a tendency for sensitivity to diminish from test to test. This tendency is less marked if glycosuria is induced.

The hyperglycemic action of adrenaline (0.4 mg. subcutaneously) in a fasting cat was only slightly accentuated when GH (2 x 2.5 mg.) was given three hours before and simultaneously with the adrenaline. When

adrenaline (0.1 mg.) was given to a rabbit similarly treated, its hyperglycemic action was unaltered. With a higher GH dose (3 x 5 mg.), given in part the previous evening, the action of adrenaline (0.05 mg.) in the same rabbit was accentuated, as in the experiments of Young in which a prolactin preparation was administered. GH had little effect on the blood-sugar level per se over a 3-hour period.

RHOADS, JONATHAN E.; LIBORO, OSCAR; FOX, SAMUEL; GYORGY, PAUL; AND MACHELLA, THOMAS E. *(Harrison Dept. of Surgical Res., Sch. of Med., Univ. of Pennsylvania, and the Surgical Clin., Nutritional Service, Dept. of Pediatrics, and Gastrointestinal Section, Dept. of Med., Hosp. of Univ. of Pennsylvania, Philadelphia):* In vivo action of a new lipotropic fraction of the pancreas. Am. J. Physiol. *166:*436-40, August 1951.

The pancreatic extract designated AI, prepared by the method of Bosshardt, Cieresko, and Barnes, exerted a marked lipotropic action at a dosage level of 60 mg. per day on depancreatized dogs maintained on insulin. The activity of the material was largely destroyed by boiling for three minutes. The fat content of the liver of fasting dogs generally rose despite the extract. The extract apparently acts in the body as an enzyme, although other workers have shown it does not in vitro.

RICHER, LUIS A. *(Asuncion, Paraguay):* NPH—A New Insulin of Intermediate Action. Imp. Ariel, Asuncion, 1951.

In 7 cases of diabetes, stabilization was accomplished with a 5 to 10 per cent reduction in the daily dose of NPH as compared with the dose of PZI or mixtures previously used.

ROUQUES, L. *(Paris):* Bucco-dental changes of juvenile diabetes and their treatment. Presse méd. *59:*1030, July 18, 1951.

Dental lesions of diabetics must be treated by meticulous removal of tartar and by treatment of caries and apical infections.

SANGER, F. *(Cambridge):* The chemistry of insulin. Chem. Soc. Ann. Rep. *45:*283, 1948.

A condensation of the recent pertinent reports on the structure and composition of the insulin molecule.

SANGER, F.; AND TUPPY, H. *(Univ. of Cambridge):* The amino-acid sequence in the phenylalanyl chain of insulin: 1. The identification of lower peptides from partial hydrolysates. Biochem. J. *49:*463-81, September 1951.

Partial hydrolysates of fraction *B* of oxidized insulin have been fractionated by paper chromatography, and the structure of the resulting peptides has been determined. It is concluded that the following amino-acid sequences are present in this fraction: Phe . Val . - Asp . Glu . His . Leu . $CySO_3H$. Gly, Thr . - Pro . Lys . Ala, Gly . Glu . Arg . Gly, Tyr . - Leu . Val . $CySO_3H$. Gly, and Ser . His . Leu . - Val . Glu . Ala.

SANGER, F.; AND TUPPY, H. *(Univ. of Cambridge):* The amino-acid sequence in the phenylalanyl chain of insulin: 2. The investigation of peptides from enzymic hydrolysates. Biochem. J. *49:*481-90, September 1951.

Fraction *B* of oxidized insulin was subjected to hydrolysis by pepsin, trypsin, and chymotrypsin. The resulting peptides were fractionated by paper chromatography, and their structure was investigated. It is concluded that the structure of the phenylalanyl chains of insulin is Phe . Val . Asp(-NH_2) . Glu(-NH_2) . His . Leu . - CyS . Gly . Ser . His . Leu . Val . Glu . Ala . Leu . - Tyr . Leu . Val . CyS . Gly . Glu . Arg . Gly . Phe . - Phe . Tyr . Thr . Pro . Lys . Ala.

SASSON, MAURICE I. *(Morrisania City Hosp., New York City):* Effects of Priscoline in diabetes: A preliminary study. New York State J. Med. *51:*1315-18, May 15, 1951.

A study was made of the possible effects of Priscoline on fasting blood sugar and also on the glycosuria of 25 diabetic patients. No significant change in fasting blood sugar was observed in 10 cases; in 5 there was a decrease; and a rise was noted in one. In the others variable changes occurred, i.e, minor increases and decreases at various times during the period of administration of the drug. Withdrawal of Priscoline was followed by a return of the fasting blood-sugar concentration to the "pre-Priscoline" value. An apparent beneficial effect of the drug was noted in the case of 3 diabetics with retinitis and marked impairment of vision.

SCHILLER, ALFRED A. *(Dept. of Physiology, Univ. of Illinois Coll. of Med., Chicago):* Mechanism of action of vitamin P flavanoid (rutin) on the cutaneous circulation. Am. J. Physiol. *165:*293-305, May 1951.

Rutin and presumably other vitamin P substances produce strong cutaneous vasoconstriction in the unanesthetized rabbit which is independent of epinephrine participation. Rutin also possesses the property of prolonging in vivo the action of epinephrine and to a lesser extent that of arterenol. In the light of these results, effects of vitamin P are discussed in relation to its property of strongly constricting minute cutaneous blood vessels.

SELIGSON, DAVID; AND SELIGSON, HARRIET *(George S. Cox Med. Inst., Univ. of Pennsylvania, Philadelphia):* The conversion of alloxan to alloxanic acid in plasma. J. Biol. Chem. *190:*647-57, June 1951.

The authors examined the nature of the decomposition of alloxan in plasma and buffered solutions. Alloxan was converted to alloxanic acid under the conditions employed. This reaction is complete or nearly so, is more rapid with increasing alkalinity, and is a rapid first-order reaction at room temperature. The conversion of alloxan to alloxanic acid was studied by the following procedures which have not been previously applied to this reaction: (a) oxidimetry with ceric sulfate, which distinguishes alloxan, alloxanic acid, and oxomalonic acid, one from the other. Alkaline hydrolysis resulted in the stoichiometric formation of oxomalonic acid from alloxan or alloxanic acid, and (b) the colorimetric determination, by a method described in the text, of oxomalonic acid.

The authors suggest that if alloxan plays any part in diabetes mellitus, its role might be further elucidated by the study of its more stable conversion product, alloxanic acid.

SHIDEMAN, F. E.; AND RENE, ROBERT M. *(Dept. of Pharmacology, Univ. of Michigan Med. Sch., Ann Arbor):* Succinate oxidation and Krebs cycle as an energy source for renal tubular transport mechanisms. Am. J. Physiol. *166:*104-12, July 1951.

In a study with four chemically dissimilar compounds (dehydroacetic acid, malonic acid, cincophen, chlorguanide), the authors report a close correlation to exist between the concentrations of these compounds required to produce significant inhibition of succinoxidase activity in vitro, inhibition of PAH (P-aminohippuric acid) or PSP (Phenolsulfonphthalein) concentration of kidney slices in vitro, and doses necessary to suppress significantly renal tubular secretion of PAH or PSP in vivo. One of the four compounds, dehydroacetic acid, has been demonstrated to inhibit markedly a second secretory mechanism which exists in the renal tubules, namely, the one involved in the secretion of N^1-methylnicotinamide.

In contrast to the above findings, these compounds (except chlorguanide), in doses which markedly suppress tubular secretion, have no significant effect on the reabsorptive capacities of the tubules for glucose and phosphate.

On the basis of these results, a schema of some of the energy sources for renal tubular transport mechanisms has been suggested, in which energy from succinate oxidation (and Krebs cycle oxidation) has been assigned a relative specificity in that it is more directly involved in tubular secretory processes than it is in the mechanisms employed for the reabsorption of glucose and phosphate.

SHUMAN, CHARLES R.; AND FRANCIS, ROBERT B. *(Dept. of Med., Temple Univ. Sch. of Med.):* NPH insulin in diabetic patients with complications. Am. J. M. Sc. *222:*179-85, August 1951.

Blood glucose curves indicated that NPH insulin was effective in the control of the postprandial blood glucose as well as the fasting glucose levels in the majority of 33 patients studied. In a few instances, it was necessary to deduct 10 to 15 per cent of the carbohydrate from breakfast in order to avoid a high postprandial rise in blood glucose. This carbohydrate was given as an interval bedtime feeding. When this failed to effect a lowering of the postbreakfast sugar, a small dose of regular insulin was administered in the syringe with the NPH preparation.

NPH insulin is a valuable preparation for the control of diabetes in patients with medical and surgical complications.

EDITORIALS

THE GLUCOSE TOLERANCE TEST

The glucose tolerance test has been used for decades to help physicians establish the early diagnosis of diabetes mellitus and to distinguish nondiabetic glycosurias. In the majority of cases of diabetes, such a test is not needed for diagnosis; as Lukens points out, the indications are infrequent.[1] It is only when routine tests of the urine and blood sugar have been indecisive that it is now considered valuable.

According to Mosenthal, the old dictum that every diabetic has a high prolonged glucose tolerance curve but that every high prolonged curve is not indicative of diabetes still holds true. The variability of the results and the lack of specificity of the "positive" glucose tolerance test have become well known to clinicians, but the usefulness of the procedure under appropriate conditions continues to receive recognition. In recent years the studies of Mosenthal and Barry,[2] Lawrence,[3] Blotner and Marble[4] and others have confirmed the value of the test and have also shown its limitations.

Mosenthal and Barry pointed out the variable and unpredictable amounts of nonglucose substances included as glucose by the Folin-Wu determination and strongly favored the use of a blood sugar method determining the true blood glucose. They pointed out further that the use of venous blood is advantageous since the sugar content of arterial (or capillary) blood shows wide fluctuations. The criteria for normal values of true glucose which they proposed are an upper limit of 100 mg. per 100 cc. in the fasting state, a maximum peak of 150 and a fall to 100 two hours after the ingestion of 100 Gm. of glucose. For the Folin-Wu determinations they gave values 20 mg. higher. This is in close agreement with, but not identical to, the information contained in the *Diabetes Guide Book* of the American Diabetes Association.[5] Here it is stated that the normal results of the sugar tolerance test usually show a rise in the venous blood sugar not over 200, and a return below 120 in two hours.

Differences of opinion have developed in regard to the choice of route of administration of glucose in the tolerance test. For the sake of convenience, most physicians follow the traditional custom of giving it orally. Some prefer to give it intravenously. In a recent paper Soskin labeled the oral glucose tolerance test a "practically worthless" procedure.[6] Soskin recommended the routine use of the glucose tolerance test by the intravenous method on the grounds of greater accuracy and also because of his opinion that such a test, performed in a standard manner, would permit differentiation of diabetes from a disorder of metabolism originating in the liver. On the other hand, Moyer and Womack[7] concluded that "The intravenous test is inferior to the oral

glucose tolerance test as an index of hepatic function and only under special circumstances is it of use as an adjunct to the oral method."

Soskin emphasized the fundamental role of the liver in the regulation of the blood sugar level and in its influence on the nature of the sugar tolerance blood sugar curve. Others have given special attention to the use of such tests in the study of various endocrine disorders affecting carbohydrate metabolism. In addition to the glucose tolerance test, the insulin tolerance test, the glucose-insulin tolerance test, and the insulin-followed-by-glucose tolerance test have been investigated.[8] Each of these procedures can contribute to the study of carbohydrate metabolism, but it cannot be claimed with certainty that they can be applied with advantage in routine clinical practice. In fact, the claim that any pattern of blood sugar curve is specific for a disorder of the liver or any other disorder may be challenged.

To a large extent these adaptations of the tolerance test still represent technics of research. On the other hand, the confirmation of the diagnosis of diabetes or the exclusion of this condition by observation of the blood sugar curve is usually a simple matter, whether the glucose is given by mouth or by vein. For this limited purpose the oral glucose tolerance test is still a procedure of definite value in selected cases.

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LABORATORY INVESTIGATION OF OBESITY

The importance of obesity in relation to diabetes has long been recognized. Information first came from a variety of clinical observations, including the common occurrence of diabetes in obese individuals, and the improvement in the diabetic state, even apparent remission, appearing after reduction of excess weight. Statistical studies have strengthened the evidence for this relationship. In a recent analysis of the weight of persons developing diabetes after the age of 40, it was found that approximately 60 per cent had previously been markedly overweight, and an additional 25 per cent had been moderately overweight. Only 15 per cent did not give a history of obesity preceding diabetes.[1]

In spite of the clinical significance of obesity, the condition has been studied experimentally only to a limited extent. Nevertheless, information of a highly significant nature has been secured. Every stock and poultry raiser knows that animals can be fattened for the market by limited activity and liberal feeding. Ingle used this plan in the experimental production of obesity in rats.[2] He found that tremendous adiposity could be induced, a rat with restricted activities attaining a weight more than twice that of a normal active rat.

Long's report in this issue concerning obesity produced in rats and in monkeys is of unusual interest.[3] As a result of bilateral lesions in the hypothalamus made by electrolysis, the animals acquired a voracious appetite resulting in the rapid development of extreme obesity. In certain cases, he noted progressive impairment of carbohydrate tolerance. He showed also that these animals became vulnerable to removal of a part of the pancreas. A partial pancreatectomy could be tolerated by the ordinary rat but was followed by glycosuria when the production of a brain lesion caused the development of obestity. These observations recall experiments conducted by Frederick M. Allen more than 30 years ago.[4] He found that a partial pancreatectomy in dogs, which had no apparent effect when they were eating in the usual way, was followed by diabetes when the dogs were fattened by overfeeding.

The recent reports of hereditary obesity in mice represent a new approach to the problem. A strain has been produced with many adult mice weighing 38 to 56 Gm., compared with the average weight of non-obese mice, ranging from 16 to 26 Gm.[5] In the limited number of cases in which tests could be made, it was found that the obese mice showed glycosuria and hyperglycemia indicating diabetes.[6] The amount of sugar in the urine

was in the neighborhood of 3 per cent; the blood sugar was usually above 200, as compared with the blood sugar level of 110 in the case of non-obese mice. In obese diabetic mice, ulcerative lesions of the skin were frequently seen. The obese rats studied by Long showed in many instances evidence of renal and vascular disease. Thus experimental obesity with diabetes tends to manifest complications similar to those seen in human patients.

In summary, the experimental studies of obesity show that while fattening depends on a caloric intake in excess of the energy expenditure of the individual, this may depend not merely on deliberate indulgence but also on a disorder of appetite resulting from an acquired or inherited disturbance in the central nervous system. They further strengthen the evidence that obesity predisposes to diabetes.

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DIABETES *LOOKS AHEAD*

With the birth of DIABETES as a new medical journal, the lives of its parents now come to a close.

In his Foreword, Dr. Joslin has pointed out the value of the annual *Proceedings* and the quarterly *Diabetes Abstracts,* which was firmly established during their ten years of existence. For the success of these publications, the Association is indebted to a number of its members; three individuals deserve special recognition. The *Proceedings* volumes were prepared by the Committee on Scientific Publications, headed for its first six years by Dr. I. Arthur Mirsky. The development of *Diabetes Abstracts* was especially the work of Dr. Franklin B. Peck, who was succeeded in 1949 by Dr. William R. Kirtley. Credit is due these men and their co-workers for the high reputation of the two publications.

Both of the predecessors of DIABETES were limited mainly to the Association's membership. The new publication will be available to all who are interested in the subject. It will continue to present abstracts of papers on diabetes and a selection of the papers presented at the Annual Meeting. In addition it will provide the Association with new opportunities for service to the medical profession.

Diabetes is a disorder which claims more than usual attention from practicing physicians, partly because it affects so many people, partly because practice with diabetic patients covers the entire field of medicine. The disease furthermore presents an unusual challenge to the investigator. In spite of the effectiveness of present day treatment there exists the hope that means may be found of bringing about reversal of the disorder, and also prevention of its complications.

The Journal will endeavor to fulfill the aims of the Association as far as they include dissemination of knowledge of diabetes, the promotion and maintenance of high standards of treatment, and the stimulation of investigation. Its contents will include material of interest to general practitioners and scientists, internists and specialists in various other fields. It will at all times keep as its primary goal the welfare of the diabetic patient.

BIOGRAPHICAL NOTE

Arnoldo Cantani

PIONEER OF MODERN DIABETES TREATMENT

Frederick M. Allen, M.D.

NEW YORK

Three men are commonly considered the outstanding pioneers in modern treatment of diabetes: Bouchardat (1806-1886) in France, Cantani (1837-1893) in Italy, and Naunyn (1839-1925) in Germany. Of the three, Cantani was foremost in his insistence that stopping glycosuria was the major method of controlling the disease.

All three men lived at a time when, after centuries of dense ignorance, there occurred an explosive outburst of scientific achievement and enthusiasm which is reminiscent of the similar excitement arising from the primitive beginnings of an atomic technology in our own time. As background for their researches in diabetes these three pioneers had Rollo's "animal food" empiricism; the physiological revelations of Claude Bernard; the discovery of enzymes and also of internal secretions; the foundation of physiological chemistry by Liebig; Pasteur's incredible bacteriology; the new microscopic anatomy opened up by the Schleiden-Schwann cell theory and followed by Virchow's cellular pathology; many metabolic studies capped by the investigation of respiratory metabolism by Pettenkofer and Voit; and—by no means unimportant in themselves—the development of methods of sugar analysis both by copper reduction and by polarimetry.

Cantani unfortunately did not live as long as Naunyn, whose nearly nine decades spanned the whole period of rapid progress from primitive beginnings to the actual dawn of the insulin era. In 1894, a year after Cantani's death, a biographical sketch appeared, with his photograph and a list of his publications.[1] According to this sketch, it was as a student in Germany that he received the full impact of the new world of medical science. In 1864, while still under thirty, he became professor of materia medica and therapeutics at Pavia, and in 1868, at thirty-one, professor of internal medicine at Naples.

His keen mind ranged over wide fields of interest in natural science and medicine. He published contributions in bacteriology, such as the infectious causation of broncho-pneumonia; a paper on the use of hypodermo-

clysis and intestinal lavage in the treatment of cholera, which grew out of his experiences with the cholera epidemic of 1884 in Italy; treatises on various metabolic disorders; and a textbook of materia medica and therapeutics (1877) "based on recent advances in physiology and clinical medicine." His insistence throughout was upon observation, both in the laboratory (including animal experimentation) and in the clinic.

This quality is brilliantly illustrated in the most important study of his life, the intensive analyses which he made of 1,004 cases of diabetes. The baffling mystery of the disease drove him to explore every part and every function of the body in an effort to find its nature and its cause. He studied all that was known of the chemistry of digestion and metabolism. He searched every detail of the clinical history and all obtainable autopsies, with particular attention to the physical examinations and the reported responses to every known treatment. He was particularly concerned with the gross and microscopic character of all the organs, including the viscera, nervous system and muscles, and incidentally he noted the peculiar changes in the renal tubules.

Inevitably, the volume of Italian lectures resulting from this study, published in 1875, was translated into French (1876) and German (1877). For more specific details of this study, reference may be made to my earlier summary of Cantani's work.[2]

The principal points which Cantani foreshadowed—or deviated from—in modern theory and practice can be briefly summarized. He was positive in his opinion that excessive eating of starch and sugar is the preeminent or at least the exciting cause of diabetes. In holding to this idea, he discarded etiologies based on nervous and traumatic incidents and a whole category of other alleged causes. He dismissed hereditary aspects on the theory that they represented chiefly a family habit of carbohydrate excess.

He recognized high blood sugar as the product of the unutilized carbohydrate of the diet and as the source of glycosuria, but he believed it to be an abnormal, non-polarizable "para-glucose." Pathologically, he placed the site of diabetes in the abdominal digestive organs, to some extent in a disordered liver or stomach but predominantly in the pancreas. This view was not related to Langerhans' discovery of the islands in 1869, but rather rested on his own observation that atrophy or fatty change of the pancreas is more frequent in diabetes than in any other disease.

Cantani noticed and utilized the reduction of glycosuria by muscular exercise, but regarded gain of weight as beneficial and thus favored high calories when possible. In general, his treatment was based on the principle of sparing a weak organ. He rejected all the medications for diabetes which were in use then and long afterwards. "The remedy for diabetes is not in the drugstore but in the kitchen," he pronounced. His diet was remarkable for its strictness. When a patient first came under treatment, he was permitted only 500 Gm. or less of cooked meat daily, with the optional addition of certain acids, especially lactic acid, which was introduced not only for flavoring but also as a carbohydrate intermediary which avoided the glucose molecule. After a period of freedom from glycosuria, vegetables and then other carbohydrates could be added as tolerated. But if the severest diet did not make the urine sugar-free, fast-days were imposed. If necessary, a patient might be locked in his room for as long as six weeks to assure his fidelity to this ordeal.

Cantani's resort to the harshest measures, when they were required, was actually a part of his principal contribution to the knowledge of diabetes—his recognition of the fact that patients did well as long as they were sugar-free, but that if they continued to have glycosuria the diabetes became worse and ended fatally.

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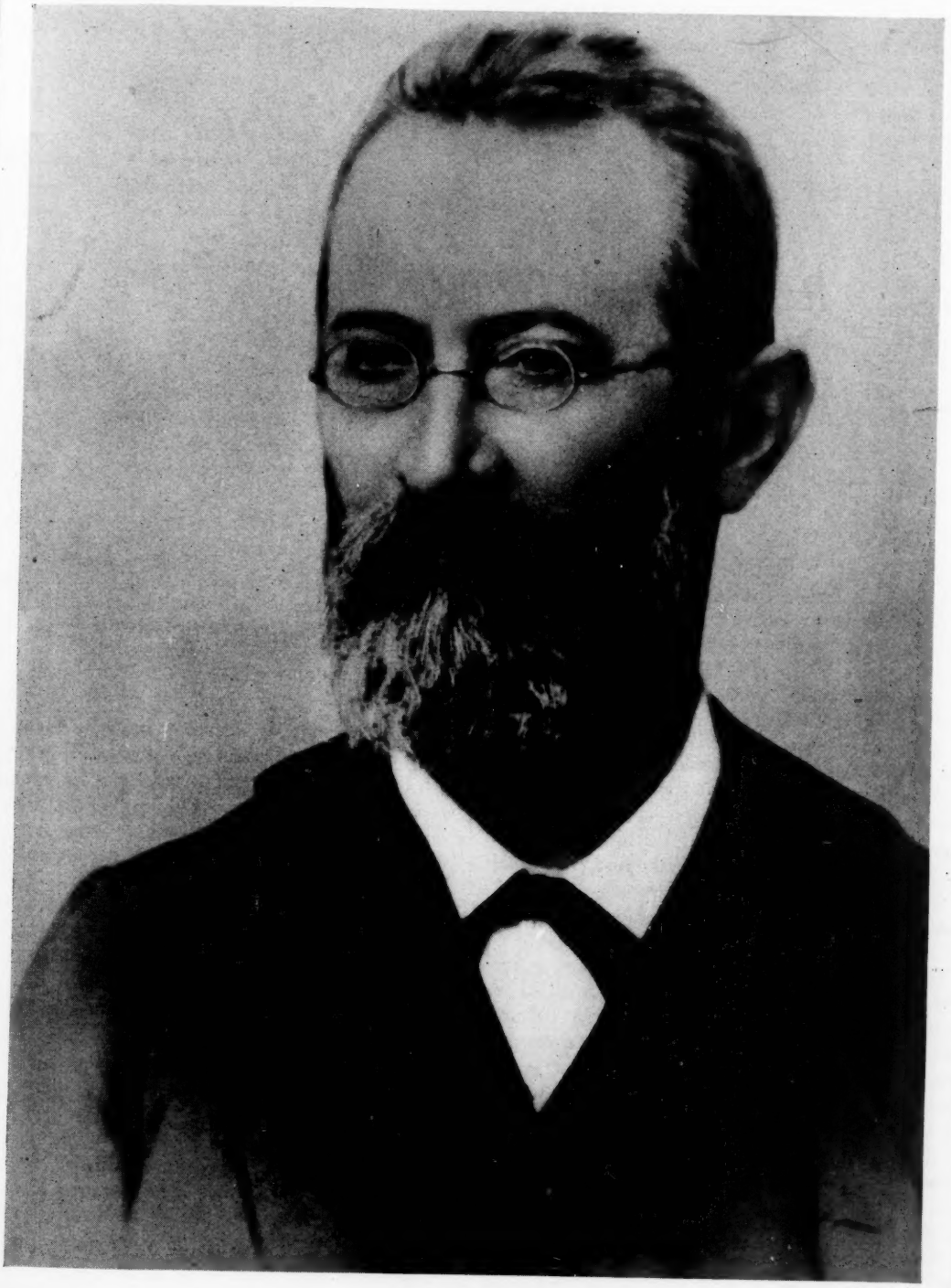


ARNOLDO CANTANI

RECENT STATISTICS

ON DIABETES

FOREWORD

The section on Diabetes Statistics is carried over from *Diabetes Abstracts,* in which it appeared regularly beginning with the tenth issue of that journal (Volume 3, Number 2) for April 1944. The section was started on the suggestion of Herbert H. Marks to Dr. William Muhlberg, then Treasurer of the American Diabetes Association and Chairman of its Committee on Statistical Investigation and Corporate Membership.

The original proposal was for a regular page on current statistics of the disease, with particular emphasis on mortality statistics. Gradually, other types of statistical data on diabetes and on the characteristics of the diabetic population were added. For a period of several years, the section consisted merely of a series of statistical tables. It was proposed in 1946 to enhance the value of this section by adding a short interpretive text with regard to the statistics contained in the tables, and this was done beginning with the first issue of Volume 6 of *Diabetes Abstracts.*

The Statistical Section of *Diabetes Abstracts* contained from the beginning the latest available data on diabetes mortality in the United States as a whole, for selected states and cities, and among Industrial policyholders of the Metropolitan Life Insurance Company, who represent a good cross-section of wage-earning families. In addition, the latest figures for two Canadian cities, for London Administrative County and for England and Wales were presented regularly; more recently current regional data for the United States were added. Credit and thanks are due to the National Office of Vital Statistics, to the health departments of the various cities and states and to the Registrar General of England and Wales for the prompt submission of their current figures on diabetes mortality. The other material presented in the Statistical Section, which has covered many aspects of diabetes, has been suggested or submitted by the members of the Committee on Statistics, although occasionally suggestions were received from other sources.

By agreement with the Editor, the Committee on Statistics of the Association plans to present new data on diabetes statistics in three or four issues of DIABETES each year. The Committee would like to remind Association members and other readers of the Journal that it welcomes suggestions or actual material suitable for these pages.

—Herbert H. Marks, *Chairman*
Committee on Statistics

TABLE 1. ***Diabetes Deaths and Death Rates, January—September 1950 and 1951***

Area	Death Rates per 100,000		Number of Deaths	
	1951	1950	1951	1950
United States (10% samples)	16.4	16.5	1,881	1,859
Metropolitan Life Insurance Company				
Industrial Policyholders	15.2	15.2	2,127	2,158
New York State	20.0	20.7	2,248	2,297
New York City	19.4	19.8	1,159	1,175
Maryland	19.9	18.3	359	322
Baltimore	21.6	21.3	154	151
Boston, Resident	25.2	26.8	153	160
Philadelphia	24.9	25.2	389	391
Toronto	15.3	17.2	76	86
Montreal, Resident	14.7	17.3	121	139
London (Administrative County)				
(first 48 weeks)			292	241
England and Wales (January-June)				
Total			2,100	1,948
Males			702	656
Females			1,398	1,292

Note: Deaths ascribed to diabetes classified according to the Sixth Revision of the International List of Diseases, Injuries, and Causes of Death. Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in *Current Mortality Analysis,* a monthly report of the National Office of Vital Statistics, U. S. Public Health Service.

TABLE 2. ***Number of Deaths and Death Rates for Diabetes by Geographic Division, United States Reporting Area for the 10 Per Cent Sample, January-September 1949, 1950 and 1951***

Geographic Division	Death Rates per 100,000			Number of Deaths		
	1951	1950	1949	1951	1950	1949
U. S. reporting area	16.4	16.5	16.0	1,881	1,859	1,775
New England	25.4	21.2	20.4	170	147	141
Middle Atlantic	18.1	20.8	20.2	415	476	453
East North Central	20.8	21.2	19.4	480	485	439
West North Central	18.2	17.5	15.9	195	187	168
South Atlantic	13.0	13.8	14.2	209	210	214
East South Central	10.6	9.4	11.8	93	80	99
West South Central	13.1	10.7	11.9	145	117	128
Mountain	10.1	7.8	10.9	39	28	37
Pacific	12.3	11.6	9.1	135	129	96

Note: Deaths ascribed to diabetes classified according to the Sixth Revision of the International List of Diseases, Injuries, and Causes of Death. These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month, but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 3 of each monthly issue of the *Current Mortality Analysis.*

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 3. ***Death Rates from Diabetes Mellitus by Color, Sex, and Age***
Metropolitan Life Insurance Company, Industrial Department, 1926 to 1950

Age Period Years	Death Rates per 100,000							Percentage Change 1946-1950 Since 1926-1930
	1946-1950	1950	1949	1948	1947	1946	1926-1930	
Total Persons								
1-74*	15.8	16.5	15.9	14.7	15.8	16.1	18.4	—14
White Males								
1-74*	10.6	11.8	11.2	9.2	10.4	10.6	13.3	—20
1-4	0.4	0.5	0.5	-	0.2	0.6	1.2	—67
5-14	0.4	0.3	0.2	0.4	0.4	0.7	1.6	—75
15-24	1.0	0.5	1.1	1.2	1.2	1.0	3.0	—67
25-44	3.6	3.9	3.9	2.8	3.6	3.8	5.2	—31
45-64	32.2	35.8	35.4	25.8	33.4	30.7	40.8	—21
65-74	123.3	141.4	123.4	117.2	110.5	124.0	126.4	— 2
White Females								
1-74*	20.5	20.5	20.2	19.5	20.9	21.2	23.4	—12
1-4	0.6	*1.0*	0.2	0.8	0.6	0.5	1.3	—54
5-14	0.8	1.0	0.6	0.8	0.5	1.1	2.0	—60
15-24	1.4	1.1	1.4	1.0	1.9	1.8	2.9	—52
25-44	3.0	2.6	2.7	2.5	3.5	3.8	5.8	—48
45-64	61.2	62.4	58.3	57.7	63.5	64.2	79.5	—23
65-74	278.3	277.5	288.0	273.0	276.8	276.0	238.9	+16
Colored Males								
1-74*	10.4	12.4	9.9	8.9	10.3	10.5	11.9	—13
1-4	*0.4*	-	-	-	*2.0*	-	*3.2*	—88
5-14	*1.0*	*0.7*	*0.7*	*2.9*	-	*0.7*	*1.2*	—17
15-24	1.8	*2.3*	*0.5*	*1.6*	*1.1*	*3.3*	2.8	—36
25-44	4.6	5.4	4.5	3.3	4.8	5.1	6.4	—28
45-64	30.9	38.0	28.5	28.1	31.6	28.3	38.1	—19
65-74	106.1	125.3	114.0	76.1	105.1	109.9	86.7	+22
Colored Females								
1-74*	23.0	24.8	23.6	24.2	20.9	21.4	23.2	— 1
1-4	*0.4*	-	-	-	*2.0*	-	*1.4*	—71
5-14	*0.9*	*0.6*	*0.6*	*1.4*	-	*1.9*	*2.2*	—59
15-24	*2.2*	*2.6*	*2.8*	*1.5*	*2.9*	*1.2*	*2.8*	—21
45-64	7.7	8.8	7.1	6.6	7.9	8.0	13.5	—43
25-44	82.7	85.1	92.3	89.1	70.1	77.0	84.0	— 2
65-74	210.4	244.1	190.8	227.2	201.3	188.7	144.0	+46

* Death rates standardized for age.

Note: Rates italicized are based upon fewer than 10 deaths.

Source: *Health Progress Among Industrial Policyholders, 1946 to 1950*, by Louis I. Dublin and Mortimer Spiegelman. Society of Actuaries Transactions, Vol. III, p. 294, Sept. 1951.

TABLE 4. ***Death Rates per 100,000 from Diabetes by Sex, Ages Under 45 and Ages 45 and Over. United States (White) and Selected Countries, Postwar Experience***

Country	Year	Males		Females	
		Under 45	45 and Over	Under 45	45 and Over
United States*	1948	1.9	67.7	2.0	111.6
England and Wales	1948	0.9	14.0	1.0	25.2
Scotland	1948	1.3	15.3	1.3	36.1
Australia	1948	1.1	42.2	1.6	78.8
New Zealand	1949	0.9	45.4	0.8	86.7
Canada	1948	2.1	55.6	1.7	91.5
Ireland	1948	1.5	15.9	1.7	15.3
South Africa	1947	1.2	35.0	1.7	50.9
Denmark	1949	1.9	52.5	1.8	71.9
Finland	1949	3.4	9.7	2.5	18.7
France	1949	1.3	18.2	1.5	27.4
Italy	1949	0.8	23.4	0.8	29.1
Netherlands	1949	0.6	20.5	0.6	45.3
Norway	1948	1.3	24.9	1.5	46.9
Portugal	1949	1.4	16.5	1.0	20.0
Sweden	1947	1.0	16.7	1.9	29.5
Switzerland	1948	1.3	23.4	1.5	39.2

*White persons.

Note: The death rates are not strictly comparable for the various countries because of differences in medical practice, in certification of causes of death and in classification procedures.

Source: *Statistical Bulletin,* Metropolitan Life Insurance Company, Vol. 32, p. 6, Oct. 1951. Abstract of paper by Louis I. Dublin, "Factors in the Higher Mortality of Our Older Age Groups."

TABLE 5. ***Underlying Cause of Death Where the Death Certificate Contained a Mention of Diabetes Mellitus, but Diabetes Mellitus Was not Coded as the Underlying Cause of Death Iowa, 1950***

Underlying Cause	Number of Deaths	Per cent of Total
Total	498	100.0
Pulmonary tuberculosis	4	0.8
Malignant neoplasms	47	9.4
Vascular lesions affecting central nervous system	87	17.5
Heart diseases	235	47.2
Hypertension (without mention of heart) and general arteriosclerosis	26	5.2
Pneumonia and influenza	19	3.8
Hernia and intestinal obstruction	4	0.8
Cirrhosis of liver	4	0.8
Nephritis (chronic and unspecified)	12	2.4
Hyperplasia of prostate	4	0.8
Accidents	21	4.2
All others	35	7.0

Source: Iowa State Department of Health, Division of Vital Statistics. Supplement of Morbidity Report for week ending Saturday, Sept. 24, 1951.

COMMENT

The recorded death rate from diabetes in the United States, on the basis of the Sixth Revision of the International List, shows little change in the first 9 months of 1951 from the corresponding period of 1950. Official data, derived from the 10 per cent sample of death certificates, show a reduction of 1 per cent, while the experience among Industrial policyholders of the Metropolitan Life Insurance Company shows identical rates for the first 9 months of both years. Local statistics for the few states and cities for which data are collected likewise indicate no significant change in the diabetes death rate in 1951 from the previous year. The two Canadian cities, Montreal and Toronto, from which data are received, show a sizable reduction—15 per cent and 11 per cent, respectively—in the rate for the 9 months of 1951 as compared with 1950. These findings are not statistically significant because the total number of deaths is relatively small.

The English data show a rather appreciable increase in the number of deaths from diabetes during 1951. The rise in the reported number of deaths in London Administrative County is particularly sharp. This may be, in part, a local situation, but the number of deaths from the disease recorded in England has been rising now for two or three years.

Regional data on diabetes mortality in the United States during the first 9 months of 1950 and 1951, based on the 10 per cent sample, show no consistent pattern, even for those areas in which the number of deaths in the sample is fairly large. In the Middle Atlantic region the death rate in 1951 is appreciably lower than in 1950 and in the East North Central states it is slightly but not significantly lower than in 1950. As for the other areas, the variations may reflect either the size of the sample or other limitations of the data to which reference is made in the footnote of the table.

Dublin and Spiegelman have recently reviewed the mortality experience from major causes among Industrial policyholders of the Metropolitan Life Insurance Company during the five-year period 1946 to 1950. The third table, derived from their paper, gives the death rates from diabetes by color, sex and age during this period, as well as a comparison with the quinquennium 1926 to 1930. Except for 1948, the age-adjusted death rate for the aggregate experience has been fairly stable during 1946-1950. The rate in 1948 was exceptionally low, actually the lowest in the last three decades. The death rates in 1946-1950 are uniformly lower than in 1926-1930, except at ages 65 to 74 among white females and among colored persons of both sexes. The reduction in the death rates is especially marked at the younger ages. In fact, the reductions in this 20-year interval exceed 50 per cent among both white males and white females at ages under 25 and is not much less at ages 25 to 44.

Dublin has assembled postwar data on mortality in the United States and several other countries in a study designed to ascertain why this country's mortality record for persons in middle and later life is comparatively less favorable than at the younger ages. The facts for diabetes are shown in the fourth table. Care must be taken in interpreting these data, first, because they are crude rates, and second, because of differences between the various countries with respect to medical practice, certification of causes of death, and classification procedures. Nevertheless, there are several interesting features in this table. For example, it is clear that at ages 45 and over the death rates from diabetes among men and women in this country are well above those of all other countries. Another major fact emerging from the table is that except for Ireland the death rates among older women are higher than those for older men. In some countries the female rate at these ages is more than double that for males.

The Division of Vital Statistics of the State of Iowa has tabulated all deaths in 1950 in which mention of diabetes appeared on the death certificate. The total was 969, or 3.6 per cent of all death certificates filed during the year. Of this total 471, or just under half, were assigned to diabetes as the underlying cause of death, in accordance with the procedure of the Sixth Revision of the International List of Diseases, Injuries and Causes of Death. This proportion held for males and females.

A tabulation was also made of the underlying cause for the 498 cases in which diabetes was mentioned on the certificate as a contributory or associated cause. As the last table shows, the cardiovascular-renal diseases accounted for nearly three-fourths of the 498 cases.

A notable feature of this Iowa experience is the high median age of those dying with or from diabetes—70.1 years.

Committee on Statistics, American Diabetes Association; submitted by Herbert H. Marks, Metropolitan Life Insurance Company, New York.

BOOK REVIEWS

DIABETES MELLITUS: PRINCIPLES AND TREATMENT. *By Garfield G. Duncan, M.D., Clinical Professor of Medicine, Jefferson Medical College, and Director of the Medical Division of the Pennsylvania Hospital and the Benjamin Franklin Clinic, Philadelphia. Cloth. $5.75. Pp. 289. Illustrated. W. B. Saunders Co., Philadelphia and London, 1951.*

This is an up-to-date, carefully written book in which the author successfully reaches his stated objective, the preparation for physicians and students of a practicable and simplified outline of the treatment of diabetes and its complications. It is not a source book of data, references or statistics, nor does it purport to be such. As a relatively brief, concise and direct guide to basic principles and treatment, it is excellent.

Throughout the book the author places emphasis on the importance of continuous, careful control of diabetes in the prevention of acute and late complications. He insists that "every diabetic patient should be diet-conscious." In planning diets, he suggests the use of the now familiar Exchange Lists prepared through the cooperative efforts of the American Diabetes Association, The American Dietetic Association and the Diabetes Section of the U.S. Public Health Service. Many clinicians will not approve of certain of the "standard diets" he lists, which contain up to 335 grams of carbohydrate a day. In fact, of eleven standard diets, five call for 260 or more grams of carbohydrate. On the other hand, the author quite properly emphasizes the importance of insuring an adequate intake of protein, minerals and vitamins.

Insulin is advised without hesitation for all patients whose diabetes is not controlled satisfactorily with diet and exercise; unless there are acute complications, an exception is made for obese patients who may be expected to improve with weight reduction. Principles for the use of various insulin programs are adequately outlined. The author regards NPH insulin as a valuable preparation. Of interest is his experience that no local lipodystrophy has occurred as long as the insulin injected is at room, rather than refrigerator, temperature. This matter deserves further controlled study.

Early chapters in the book take up in readable style fundamental matters such as definition, history, incidence, etiology, prognosis, insulin, physiology, pathology, laboratory methods, symptoms and signs, diagnosis and basic food requirements. The opinions expressed are standard and allow little room for disagreement. Chapters on acute and late complications and their treatment are well written. In the treatment of coma, the giving of adequate amounts of insulin and fluids is stressed. Glucose is not advised during the first six hours of treatment. The administration of alkali is allowed, but is considered usually not necessary. In one case reported in detail, although the giving of sodium lactate was followed by a rise in blood carbon dioxide combining power and by improvement in breathing, the plasma acetone bodies were not appreciably affected. The comment is made that this illustrates one means by which alkali therapy may, on the surface, be misleading.

The author reports excellent results in diabetic neuropathy with injections of vitamin B_{12}. There certainly would not be general agreement on this point. In the management of pregnancy in diabetes, the problem of fetal mortality is recognized. The correction of hormonal imbalance with large doses of estrogen and progesterone is endorsed. The final chapter on "The Diabetic Child" is well written and complete, though brief. An optimistic outlook for the future is preserved. Incidentally, the re-

viewer agrees with Dr. Duncan that the term "brittle diabetes" is a poor one; "labile" or "unstable" describes better the fluctuating character of the diabetic state of certain patients, particularly children.

HANDBOOK OF NUTRITION. *Prepared by various authors under the auspices of the Council on Foods and Nutrition of the American Medical Association. Second edition. Cloth. $4.50. Pp. 717. The Blakiston Company, Philadelphia, 1951.*

The latest edition of this book should be welcomed by clinician and laboratory scientist alike. A wealth of information has accumulated in the eight years since the first edition was published. The inclusion of many of the new developments in the fields of amino acid and protein metabolism, the vitamins and therapeutic nutrition, and especially the valuable lessons from the last war, make the volume both timely and appropriate.

Like its predecessor, it is a comprehensive and authoritative review of the facts on which the science of nutrition is based, written by a distinguished group of experts. Part 1 is devoted to the basic biochemistry and physiology of the essential components of food. Part 2 outlines the nutritional needs of man in health and disease, while Part 3 describes the nutritional deficiency states. Part 4 covers the adequacy of the American diet, with considerable discussion of ways in which our diet might be improved. The chapter on foods for emergency use is especially timely.

Diabetes is discussed specifically in only a brief way, but those interested in the subject will wish to read this book as a means of bringing their general nutritional knowledge up to date. A thorough understanding of diabetes necessitates a rather complete working knowledge of nutrition. The chapters on fats and carbohydrates in particular contain information of both practical and theoretical interest. The role of insulin in carbohydrate metabolism and the function of insulin in the homeostatic mechanisms controlling blood sugar are also summarized.

Only a few criticisms can be made. A few of the sections are already out of date, a fault common to most textbooks. None of the chapters deals specifically with obesity, one of our most important nutritional problems by virtue of its apparent effects on diabetes and many other chronic diseases. Those interested only in the therapy of diabetes and other conditions will find little satisfaction in reading this book. However, for those who want to understand what actually goes on in their patients, and who seek authoritative information on the new aspects of nutritional science, it contains valuable information.

THERAPIE DES DIABETES MELLITUS, EIN LEITFADEN FUR PRAKTISCHE ARZTE UND STUDENTEN DER MEDIZIN, *von Dr. Med. Georg R. Constam. Zurich (Switzerland). Cloth. Leinen Fr. $16.50. Pp. 291, with 16 illustrations. Benno Schwabe, Basel, Switzerland. Distributed by Grune & Stratton, Inc., N.Y.*

This concise textbook gives a comprehensive survey of all aspects of diabetes, including the physiology and pathology of carbohydrate metabolism, the clinical characteristics of the disease, the laboratory procedures employed in diagnosis and in guiding treatment, therapy with diet and insulin, and the various complications.

The author's ideas concerning treatment are generally in agreement with the most common practice in the United States. He stresses the importance of dietary management, but urges simple methods eliminating mathematical technics. The meal plans presented show how European food habits differ from those in America. The problems of insulin therapy are considered in detail. Mention should be made of a useful table listing 38 points for the differential diagnosis of diabetic coma and hypoglycemic reaction when caused by rapidly acting insulin, and by slowly acting insulin.

Constam aims for control of glycosuria and hyperglycemia when possible. In discussing the "free diet" he concludes that it is undesirable and unsafe, except as a temporary expedient in certain situations. Constam makes clear that his objective in treatment is not merely to maintain life, but to give protection against complications and furthermore to enable the patient to get, as far as possible, full enjoyment out of living.

An attractive feature of the book is the extensive list of references at the end of each chapter. They show familiarity with the world literature concerned with diabetes. These references can broaden the scope of physicians who are familiar only with papers written in English. The book merits widespread study.

ORGANIZATION SECTION

The Objectives

of the American Diabetes Association

DEFINITIONS AND PROPOSALS

Arthur R. Colwell, M.D.
CHICAGO
PRESIDENT, AMERICAN DIABETES ASSOCIATION, 1951-1952

At the end of its first ten years of rapidly expanding growth, the American Diabetes Association has recently completed a review of its past, an examination of its present, and a tentative program for its future. This intensive self-study was prompted by the fact that the Association's work has accumulated faster than its ability to plan. On occasion, our facilities for execution have actually lagged behind the responsibilities we have assumed.

There is understandable reason for this—for, while there has been no reasonable doubt about our fundamental purposes, the best policies to be followed for their realization have never been closely defined.

Consequently, in June 1950, the Council of the Association authorized the creation of a Committee on Purposes and Policies. This Committee was to be composed, insofar as possible, of members representative of all talents and interests within the Association, and was charged with the task of re-evaluating our purposes and defining the means of their attainment. A committee of eight (later nine) was appointed by the President. It conducted a thorough study during the following year and submitted its report in June 1951. This was approved as a working pattern for the Association, and is here summarized by the Committee's chairman.

PURPOSES

As stated in our Constitution and as described by the first President of the Association, our declaration of purposes needs little revision and no important redefinition.

Fundamentally, improvement in the welfare of diabetics everywhere should remain our principal objective, whether this be accomplished by research and investigation, education of the profession and the laity about diabetes, instruction of diabetics themselves, promotion of new facilities for study and care of the disease, or any other conceivable method. In other words, organized effort to help diabetics is our primary and undisputed function. Principles, policies and methods of doing this, however, require definition.

POLICIES

Three specific areas in which our basic purposes can be promoted seem apparent. They are (1) education of the medical and allied professions; (2) education of

An abridged summary of the recommendations of the Committee on Purposes and Policies, as approved by the Council of the Association in June 1950. Membership of the Committee: Joseph T. Beardwood, Jr., M.D., Philadelphia; Charles H. Best, M.D., Toronto; Arthur R. Colwell, M.D., Chicago (Chairman); Jerome W. Conn, M.D., Ann Arbor; Francis D. W. Lukens, M.D., Philadelphia; Franklin B. Peck, M.D., Indianapolis; Howard F. Root, M.D., Boston; Randall G. Sprague, M.D., Rochester, Minn.

the public, both diabetic and nondiabetic; (3) research Certain specific decisions and recommendations concerning activities in each of these fields seem both desirable and feasible at this time.

Professional Education

An active and continuing campaign of education within the medical and allied professions must be carried on. This should include the publication of a new scientific Journal, part of which should be our existing abstract service. The Journal should be devoted to both clinical and investigative subjects. It is a pleasure to note that this report of our Committee is actually appearing in the first issue of such a Journal.

Other aspects of the professional educational work which the Association should undertake include the preparation of scientific programs for the profession with a selection of papers similarly broad in scope, the encouragement of and participation in postgraduate courses, and the preparation and distribution of scientific exhibits of good quality.

In addition to administering these projects at the national level, the Association should also promote appropriate membership and program development in the Clinical Societies of Affiliate Diabetes Associations in the various regions of the country by the establishment of an active field program. This program should emphasize contact, coordination, mutual exchange of ideas, and the guidance of local groups by national headquarters.

Public Education

Authoritative health information about diabetes should be disseminated to the public by means of a variety of mechanisms.

Established channels of public information should be utilized for the release of conservative and sound information about diabetes. In doing so, fear techniques must be avoided and the physician-patient relationship encouraged.

Constructive development and expanding distribution of the lay magazine for diabetics, the *A.D.A. Forecast,* should be promoted by means of constant efforts to improve its quality, widen its appeal, and increase knowledge concerning it among diabetics everywhere.

An efficient pamphlet, reprint and letter service for prompt reply to inquiries about diabetes from the public should be developed immediately within the National Office.

The program for early discovery and treatment of diabetes, and for the return of the neglectful diabetic to his physician, should be continued and developed. The basic fact that the best methods of detection and treatment depend upon the cooperation of physicians, both individually and through their medical organizations, must be stressed.

Lay Societies of Affiliate Diabetes Associations should receive guidance in program and membership activities from a field service working out of the National Office and cooperating with local groups of clinicians.

Other major objectives in a public educational campaign should be the encouragement of employment of diabetics, the preparation of exhibits for the general public, and the establishment and maintenance of camps for diabetic children. Such projects can be important activities for regional or city-wide lay groups, guided by the Clinical Societies which should themselves be advised by representatives of the National Association.

Cooperative endeavors with other agencies interested in informing the public about diabetes should be continued. However, it should always be clearly understood that the name of the Association cannot be used without its full knowledge, approval and supervision in each instance.

Research

We must foster and promote research in diabetes and allied fields continually. We must solicit and accept support for such research, and administer its use through a special permanent committee responsible to the Council of the Association.

General

For the present, at least, we should not become a voluntary health agency, nor engage in public fund-raising. Sustaining financial support must be provided, preferably by the active solicitation of many corporate memberships. Our over-all program must not, under any circumstances, proceed too far in advance of financial support.

In order to reach the largest possible number of professional people, and at the same to distinguish between various degrees of experience and training, revisions in our membership classifications are necessary, and should be worked out at the earliest possible moment.

Specific measures should also be explored and put into effect to insure suitable representation of active members of the Association on our governing boards and committees.

Some of these general recommendations require constitutional revision, This is specifically true in the case of the proposals for changing membership qualifications, improving Affiliate Association relationships, and assuring supervision of all activities by physicians.

Finally, a policy committee which is representative of the membership should be reconstituted periodically to review the aims, policies and activities of the Association, and to make recommendations to the governing body concerning the most desirable future courses to be followed.

CONCLUSION

The present Committee on Purposes and Policies realizes that it has not submitted any specific changes in organization, rules or methods, even though some are necessary if the policies recommended are to be activated. It has deliberately refrained from doing so, since it was appointed to define policy but not to devise methods. Suitable committees, such as those on Constitution, Membership and Finance, exist for the purpose of preparing such changes.

The Policies Committee's conception of the Association's most effective functions now and in the foreseeable future, as it appears to its members at this time, has been presented above. The Committee hopes that this abridged report will help to keep our members and the public informed about the thinking and the plans of the Association's governing body, that it will establish improved confidence in the Association's methods of operation, and that it will above all contribute to the welfare of people with diabetes the maximum of which our Association is capable.

Address of the President

PRESENTED AT THE ANNUAL BANQUET, JUNE 9, 1951
ELEVENTH ANNUAL MEETING, AMERICAN DIABETES ASSOCIATION
ATLANTIC CITY, NEW JERSEY

Lester J. Palmer, M.D.

SEATTLE
PRESIDENT, AMERICAN DIABETES ASSOCIATION
1950-1951

It is the privilege as well as the duty of the President, at the termination of his year in office, to present an accounting of the current state of the Association. At the same time he is given an opportunity to reflect upon the past and to appraise future hopes and plans.

This Association represented, in its beginnings more than ten years ago, the fulfillment of a dream of a small group of men who realized that diabetes was becoming an ever more urgent national health problem. By the end of its first decade, the Association's usefulness has become obvious to all. Everywhere one finds a growing awareness of the increasing number of known diabetics in our population and of the fact that there are still other hundreds of thousand of unknown diabetics awaiting diagnosis. This makes our Association a constantly more essential part of the nation's drive for good health and against disease.

In the past, under the leadership of able and hard-working officers, we have made substantial progress in the carrying out of our three major objectives: education, case finding, and research.

The educational programs for both the laity and the

profession are advancing steadily. They include expanding activities in the information field, plans for postgraduate courses, and a number of new developments concerning our publications. Great progress likewise has been made in our case-finding work as a result of the efforts of our Committees on Diabetes Detection during the past three years. To research, however, it has been possible thus far to give little more than moral support, because of limited funds. We hope that increased financial support in the future will enable the Association to step up its research activities very considerably.

Some of the important events in the Association's life during the past year include: the Association's affiliation as an active member of the National Health Council; the reorganization of the Editorial Staff of the *A.D.A. Forecast;* the centralization of all organizational and publications activities in the National Office in New York City under the capable direction of the Executive Director; and the plans for replacing the quarterly *Diabetes Abstracts* and the annual *Proceedings* with DIABETES, The Journal of the American Diabetes Association.

As regards the work of our Committee on Diabetes Detection, I believe it to be an essential, effective and praiseworthy activity. Three years of diabetes detection work have proved that the individual physician is capable of valuable service in this field. I am convinced that we in the profession must take and maintain the lead in this important case-finding activity if we are to preserve the most precious feature of ethical medical care, namely, the doctor-patient relationship under a system of practice which insures free choice of physician.

The activities of certain other committees of the Association are also worthy of special mention at this time. For example, the Committee on Emergency Medical Care has been maintaining close and constant liaison with all governmental agencies that bear any responsibility for the welfare of the civilian population under conditions of war or catastrophe. Its work will continue on an expanded basis. The Committee on Employment is actively studying the problems of the diabetic in business and industry and will be making important recommendations in the near future. The Committee on Affiliate Associations has been analysing the problems of our Affiliates, and is recommending a special program for the strengthening and expansion of these organizations. This program will involve the employment of a professional field representative to serve as a skilled adviser in all matters pertaining to the health and welfare of our Affiliates. Finally, the Committee on Professional Education has continued developing its splendid joint activity with the Association for the Study of Internal Secretions, the organization of annual Postgraduate Assemblies in Endocrinology including Diabetes. This year's Assembly takes place July 2, 1951, in Seattle, Washington, and should be as inspiring and informative as the first cooperative Assembly, which was held in Miami last year.

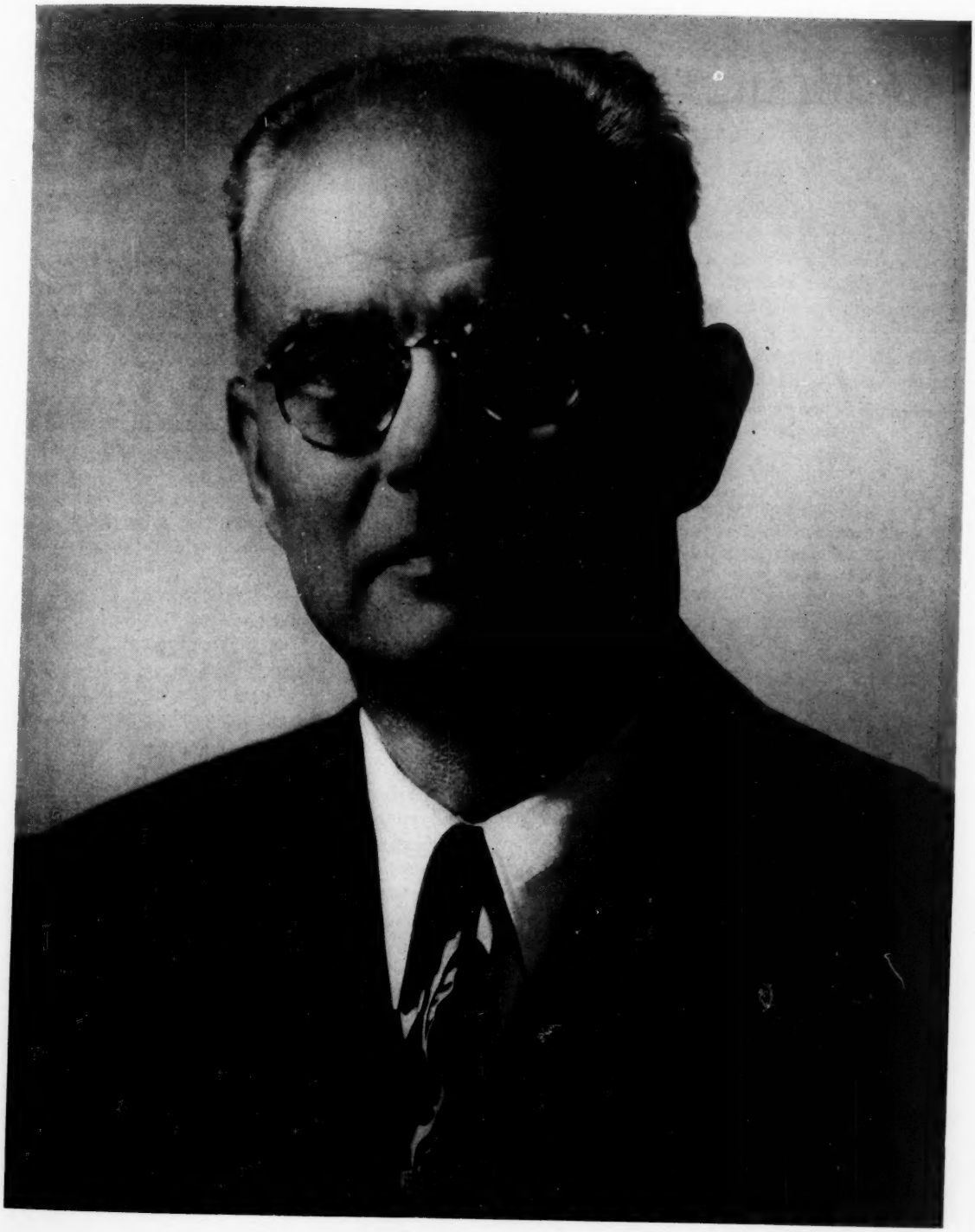
Now let me emphasize the principles which I hold to be of greatest importance to the success of our Association. First, I would like to repeat the statement of one of our past presidents that, although our primary interest as physicians may be in diabetes, we still must strive to avoid overspecialization. Let us forever remember that we are treating patients—human beings—and not just a disease alone. We have a responsibility to administer to the patient as a whole.

Second, our ultimate reason for existence as an Association is the betterment of the condition of the diabetic individual—no more, no less. I am convinced that all means leading toward that end are justifiable so long as they do not tend toward abdication of the American Diabetes Association from its role of leadership in the field of diabetes.

A final imperative for us is that we must promote more energetic research in diabetes and the field of metabolism. We must not think of diabetes solely in terms of management or control. We must as an Association attempt to extend our support of research into the questions of cause and prevention.

In closing, I wish to extend the appreciation and the gratitude of our Association to the organizations, companies, and individuals who have given us material and moral aid. Without this assistance in past years we could never have grown to our present creative and influential maturity. We hope that we will continue to merit the support of our friends.

It has been with sincere humility and with great appreciation of the honor given to me that I have served as your President. Every officer, every member of our Council and our Committees, must know how very highly their President has valued their capable and enthusiastic assistance. Without it, the progress that has taken place during this year of my stewardship could not have been even remotely achieved.



LESTER J. PALMER, M.D.

THE DIABETIC AND CIVILIAN DEFENSE

STATEMENT BY THE COMMITTEE

ON EMERGENCY MEDICAL CARE

OF THE AMERICAN DIABETES ASSOCIATION

Membership of the Committee on Emergency Medical Care:

Franklin B. Peck, M.D., Indianapolis, Chairman
Charles H. Best, M.D., Toronto, Insulin Supplies
Henry B. Mulholland, M.D., Charlottesville, Chairman, Subcommittee on Treatment
William H. Olmsted, M.D., St. Louis, Chairman, Subcommittee on Nutrition
Edward L. Bortz, M.D., Philadelphia, liaison with other agencies
Lester J. Palmer, M.D., Seattle
John A. Reed, M.D., Washington, D.C.
J. Richard Connelly, New York, Secretary

The need for adequate measures to provide for the health and welfare of the one million known (and estimated one million unknown) diabetics in this country as part of the national security program has been recognized by the Association since 1950. Approximately 70 per cent (700,000) of the diabetics in the United States take insulin daily. Many of them would die in a short time if insulin were not available. The need for prompt and effective treatment of casualties in this group would become particularly critical in the event of a major catastrophe, since they would be utterly dependent on a continuing and possibly increasing supply of insulin to protect them from acidosis, coma, and probable death.

Provision for adequate care of diabetics has been planned as a part of any emergency mobilization activity. An attempt has been made to foresee all medical, surgical, and pediatric conditions presenting dietetic and nutritional problems among the diabetic casualties and evacuees as well as the general problems precipitated by national emergency conditions.

Diabetics can play a role in total emergency mobilization almost as important as that of nondiabetics. Although not eligible for military service, they are employable and form an integral part of the total manpower reserve. Furthermore, they are experienced in the use of hypodermic instruments and this would make them valuable in caring for other diabetics or as auxiliary nursing aids. Maintenance of their health and morale is, consequently, a vital necessity. Their morale and that of their families will best be sustained, if adequate measures are taken for their protection. The Committee's primary responsibilities in approximate order of importance have therefore been to study and plan for: (1) insulin storage, supply and distribution in both target and non-target areas; (2) medical treatment of diabetics in any major emergency; (3) nutrition for the diabetic population; and (4) dissemination of information concerning the arrangements.

Present plans involve maintenance of close liaison with the Federal Civil Defense Administration. Conferences have been held with other governmental agencies, including the U.S. Public Health Service, the Federal Security Agency, the National Security Resources Board, and others interested in the problem. The Association is also working with the Council on National Emergency Service of the American Medical Association and the National Health Council.

1. INSULIN SUPPLIES

The present inventories of insulin in this country are at an all-time high level and would be sufficient to meet anticipated needs for at least two years. The industry

Abridgment of special article published in *The Journal* of the American Medical Association, December 1, 1951.

has long been cognizant of the problem and has independently taken steps to protect bulk stores of insulin and to activate emergency manufacturing lines, if present facilities were to be destroyed.

Methods of distribution in the pharmaceutical industry are well adapted to meeting the needs of a temporarily isolated segment of population, since hundreds of well-stocked wholesale and branch distributing outlets are maintained throughout the United States. Each of these normally serves as a nearby storage point for emergency needs at all times and is so organized that its individual stockpile of insulin preparations is properly stored and does not become outdated. A conservative estimate is that these outlets maintain a 30 to 60 days' supply for each area. Furthermore, the retail pharmacies of the country provide additional storage for another 15 to 30 days in advance of current needs. To this backlog must be added another 30 days' supply actually in the hands of diabetic patients. Thus normally enough insulin appears to be widely disseminated at local levels to provide for 60 to 90 days at current rates of usage. The logistics of moving these supplies into disaster areas and augmenting the supplies from larger storage points obviously becomes the responsibility of the over-all civilian defense program.

Owing to the nature of insulin preparations and the legal standards which have been set up for their storage, stockpiling of insulin in the ordinary sense does not appear practical at the present time. Stocks of insulin must be kept constantly refrigerated, above freezing and below 59° F., and must be moved at sufficiently close intervals into the market to prevent loss on account of expiration of legal storage periods or deterioration. The industry itself is thus in the best position to meet the responsibility of providing adequate supplies and has given every assurance of complete cooperation in this respect. Means for transferring supplies from area to area should, therefore, be immediately incorporated into the over-all civil defense program.

2. TREATMENT OF DIABETICS IN DISASTER AREA

It is believed that 1 per cent of the population are diabetics and that another 1 per cent are undiagnosed diabetics not heretofore under medical care. Diabetes often becomes more severe in the presence of an injury, shock, burn or infection. It is assumed, therefore, that roughly 2 per cent of the casualties would be diabetics, 1 per cent known and 1 per cent unknown. It is also apparent that many of the diabetic casualties not requiring insulin previously will come to need it as a result of their injuries or of shock. Identification of these cases will be difficult and, on this account, the recommendation has been made to governmental authorities that any program of "tagging" the population with blood groupings and other information for medical treatment include a designation for the known cases of diabetes.

Pre-Disaster Training of Diabetics

The urgency for the immediate education and training of civilians in preparation for a possible attack is admitted by all familiar with the problem. It is proposed that instructions for diabetics should be in a simple form, suitable for printing as a handbill. An example is suggested on page 85.

In addition to the cases of known diabetes, potential diabetes may become active, and in mild cases, formerly controlled with diet alone, injury, burns or shock may cause a need for insulin for management and prevention of coma. About two-thirds of the diabetic population requiring insulin use protamine zinc insulin or some other long-acting preparation, and one third use regular or crystalline insulin. Both types will be available, so the usual regimen can be continued.

Casualties

In case of injuries from mechanical causes, fire or radioactivity, regular insulin should be used in most instances, either alone or supplementary to protamine zinc insulin or other available long-acting insulin.

For routine guidance, the urine test will have to suffice. Benedict's solution is stable enough to permit stockpiling; there should also be reserve supplies of syringes and needles. For a readily available source of heat, canned heat or hexamine tablets should be available.

The shortage of blood and plasma may be acute. Without blood and plasma, and the facilities, supplies, and skills required for intravenous therapy, recourse could be had to oral administration of tolerated quantities of salt (1 level teaspoonful), soda (½ teaspoonful), and water (1 quart) as first-aid treatment of burns.*

The time-honored rule of thumb for emergency insulin dosage should be helpful. Test the urine for

*At the request of Dr. Russell M. Wilder, a Member of the Editorial Board, Dr. Sanford M. Rosenthal of the National Institutes of Health gave the following recommendations:

1. In severe burns, from 7 to 10 liters should be administered to an adult in the first 24 hours following injury.
2. If unable to administer fluids by mouth because of collapse or other reason, the intravenous route must be used, employing saline or a physiologically balanced salt solution.
3. If blood, plasma or other intravenous fluids are administered, give correspondingly less saline by mouth. *Ed.*

sugar. The doses indicated by results of the Benedict's test are as follows:

neg. (blue)	=	No insulin
1+ (green)	=	5 units insulin
2+ (yellow)	=	10 units insulin
3+ (brown or orange)	=	15 units insulin
4+ (red)	=	20 units insulin

These amounts indicate the approximate dosage of insulin necessary to control glycosuria. When the immediate emergency is over, this dosage should be administered prior to each meal, and thereafter be suitably adjusted to secure sugar-free urine specimens approximately three hours after eating.

The likelihood of decrease in insulin requirement after control of glycosuria and recovery from injury should be kept in mind. Insulin reactions should be looked for, and when they occur an appropriate readjustment of the dose should be made.

Evacuees

All doctors will be busy with the seriously wounded and obviously there will be no opportunity for medical supervision of dietary problems. Dietitians and their aids must be trained to deal with them. The diabetic should have some idea as to where to go and should try to exert some choice in the food he eats.

Many will find homes or be evacuated by civil defense authorities to other cities. There will remain some who will have to be housed and fed. In emergency shelters, dietitian aids could assist the diabetics in their choice of food and in the testing of the urine.

Patients who have no syringes should report to civil defense health services for assistance.

If dietitian aids are available, the plan for caring for diabetics and other evacuees needing dietetic help could be flexible.

3. DIABETIC DIETS IN WARTIME

Administrative Problems

Thousands of injured people would be too sick to feed themselves. In fact, the most important factor is to have someone to see to it that they eat what is presented to them. In the case of a diabetic, this is doubly important. It is proposed, therefore, that civilian dietitian aids be trained to serve food and feed the patient when necessary, in addition test urine and, under supervision, give insulin.

Civilian defense training programs should take advantage of the skills of graduate dietitians. Many of them have had duties requiring teaching experience. Graduate dietitians should be given a special course prepared by the director of nutrition and his aids, the latter to be physicians with practical experience in the administration of diets. The dietitians should be trained particularly in the problems of the hospital patient.

Civil defense organizations should also recruit young women of at least high school education who are interested in dietetics for training as dietitian aids. Instructors from the local association of dietitians, selected by the director of nutrition, should conduct classes, teaching how to serve sick people and persuade them to eat, and explaining the principles underlying the diets which have to be planned. In addition, instructions should be given in regard to the examination of the urine and administration of insulin.

Wartime Food Restrictions and the Diabetic Diet

Many diabetics, particularly those past fifty, are overweight. It is important for the physician to urge them to reduce. Reduction improves the health of the diabetic and increases his productivity.

FAT SHORTAGES. The diets of the general population during wartime contain more carbohydrate and less fat than usual. The diets prescribed for diabetics by most physicians have a higher proportion of fat. In the event of rationing and a scarcity of fats, the Committee believes that physicians should have the privilege of prescribing fats in diabetic diets to the extent of meeting 35 per cent of the caloric requirement, if considered advisable in the individual case.

RATIONING AND DIABETIC DIETS. During the past war, fats, meats, sugar and canned foods were rationed. Meats and other protein foods are more important to the average diabetic than to the nondiabetic because of the limited consumption of cereal products usually prescribed. Allowance of extra rations is therefore desirable. In particular, extra fat rations are justifiable, if the diabetic is not obese and if his caloric requirement is above 2,000.

It is unlikely that water-packed fruits will be available in wartime. Diabetics should be aware of the desirability of home canning of both fruits and vegetables. If there are wartime restrictions on enriched cereals, diabetics should be allowed more canned vegetables than nondiabetics.

The Diabetic and the Atomic Bomb

Read the Government's small pamphlet called "Survival Under Atomic Attack." Get it from your Civil Defense organization. *Read it!*

Carry your diabetic identification card with you at all times. If you have not yet secured one, your doctor can get one for you.

WHERE TO GO

In the event of an atomic bomb attack on your city, the chance of you and your home escaping injury is very good. If, however, you are within the destructive range of the bomb, you could either be injured or uninjured, but your home would probably be partially or entirely destroyed. If you are injured, you will be cared for and your diabetic condition will have attention—rest assured of that. If you are homeless and you have friends who will care for you, you need not worry.

PREPARE TO TAKE CARE OF YOURSELF completely if you are uninjured. Your family and friends should be taught enough about diabetes to take care of you in an emergency.

INSULIN

EVERY DIABETIC SHOULD KNOW HOW TO TAKE INSULIN. There is plenty of insulin. Every diabetic taking insulin should have his usual ONE EXTRA BOTTLE in addition to current needs and ONE EXTRA INSULIN SYRINGE with two needles. This is because insulin is your best friend and with it you have the best possible insurance.

Always use your oldest bottle first. For emergency purposes regular insulin is superior to the other forms. Carry a little case with your insulin syringe, if you have one.

If an emergency arises and you must change from long-acting insulin (protamine zinc insulin, globin insulin, or NPH insulin) to regular insulin, take 2 doses of the regular; for the morning dose take 3/5 of the number of units of your usual dose of the long-acting insulin, and for the evening dose take 2/5.

If you have no food, reduce your dose to 1/2 or 1/3 of these amounts to avoid insulin reactions. Test your urine.

EMERGENCY DIET

Keep to your diet as nearly as possible in all circumstances. It is better to eat too little than too much. Here is a simple emergency diet one can get under most any circumstances:

Breakfast	*Noon and Night*
Bread, 2 or 3 slices	Meat or cheese sandwich
Butter or margarine	or
Coffee and canned milk	Bread and butter alone, 3 slices
or	or
In place of bread, a cereal and a can of milk	Meat and potatoes, with such vegetables as are available (stew)

You can get along on this simple fare for several days, if necessary.

It is evident that the special requirements of our diabetic population must be integrated into the civil defense program as a whole if this large segment is to be protected and maintained in its normal state of productivity in the national effort. The government services have already demonstrated their awareness of the problem, as have the National Health Council and the Council on National Emergency Medical Service of the American Medical Association. Our purpose here is not to discuss the logistics of procuring and distributing food and insulin to these thousands of potential diabetic casualties, but to point out their special needs so that measures for their care can be formulated and incorporated into the civil defense plans—Federal, state, and local.

For general information, the book entitled "Health Services and Special Weapons Defense," prepared by the Federal Civil Defense Administration, should be consulted. *Ed.*

ASSOCIATION NEWS

TWELFTH ANNUAL MEETING AMERICAN DIABETES ASSOCIATION

The Twelfth Annual Meeting of the American Diabetes Association will take place in Chicago, Illinois, on Saturday and Sunday, June 7 and 8, 1952. It will, as usual, immediately precede the Annual Session of the American Medical Association, which will be held June 9 through June 13 in the same city.

Headquarters for the American Diabetes Association's Meeting will be the Hotel Drake, Lake Shore Drive and Upper Michigan Avenue. This is one of Chicago's outstanding hotels, and excellent accommodations both for individual physicians and their families and for large Association assemblies and smaller Committee meetings are assured.

The most important aspect of this Annual Meeting, as of all previous meetings of our Association, will be its Scientific Sessions. The Committee on Scientific Programs, consisting of Randall G. Sprague, M.D., Chairman, F. D. W. Lukens, M.D., and Jerome W. Conn, M.D., has already made considerable progress toward shaping a preliminary outline of the papers to be presented, and hopes to be able to announce a tentative program in the second issue of DIABETES, with the final program to be published in the third, or May-June, issue.

Meanwhile the Committee is still actively interested in receiving possible contributions for the Scientific Sessions. Abstracts of papers to be considered for these Sessions should be sent to the Committee, care of the National Office, by February 15, 1952. Abstracts should contain sufficient information to impart the meaning of the paper, but should not exceed 350 words.

All Association members were mailed announcements of the Annual Meeting last November, together with a hotel reservation card and an explanation of the methods of reserving rooms for the Association's sessions alone or for them and those of the American Medical Association as well. If additional copies of this announcement and the hotel reservation card are desired, they may be obtained from the Executive Director, American Diabetes Association, 11 West 42nd Street, New York 36, N.Y. Hotel reservations should, of course, be made well in advance of the meeting; and if you have mislaid your reservation card, please write for a new one at once and then place your reservation as

suggested in the announcement which will accompany the card.

Like all previous sessions, the Twelfth Annual Meeting is unquestionably going to be a memorable and worthwhile event. Association members always have an opportunity to learn the very latest—and often heretofore unannounced—results of clinical and laboratory research in diabetes and related fields; they have a chance to meet each other, too, and to discuss mutual problems and programs and renew old acquaintances, both professional and social. Every member of the Association should endeavor to attend the 1952 meeting and, if possible, bring wife and family.

THE A.D.A. FORECAST

Early in December the Association's bimonthly magazine for lay diabetics, which is its outstanding current activity in the field of patient education, had its largest week for *new* subscriptions. In the single five-day period, 304 brand-new subscriptions were recorded.

As this figure might indicate, the circulation is slowly but surely climbing. This is due to the new editorial policies and promotional activities formulated during the past year under the aegis of the *Forecast's* Editor in Chief, Frederick W. Williams, M.D. The January 1952 issue, with which the fifth year of the publication's life opens, presents a very different and new appearance, with a sunshine-yellow cover and a new logotype. The new color inaugurates a policy of changing colors on the covers of each issue in a given year, both for the purpose of adding interest and variety to the magazine, and also of making it easier for different issues to be identified.

The influence of the *Forecast* is unquestionably spreading, too. Barnett Greenhouse, M.D., of New Haven, had an excellent simple discussion on obesity in the May 1951 issue of the magazine; it was reprinted nearly in its entirety in the October 1951 issue of *Magazine Digest,* thus spreading the sound information in this article among a much wider audience. The November 1951 issue of *Life and Health* reprinted most of an early (November 1948) *Forecast* article by Charles H. Best, M.D., entitled "Diabetes and Insulin."

In addition, hardly a foreign diabetes journal for laymen comes in that does not carry within it one or more articles from the *Forecast,* sometimes translated into languages such as Dutch, Norwegian, Swedish, Italian and French. It is important that so much of the highly valuable patient education material published in the *Forecast's* pages is made available to readers elsewhere in the world of today.

DIABETES WEEK, 1951

Although it is far too early for any actual record of the number of tests made and new diabetics discovered, it is not premature to announce that Diabetes Week 1951 was, according to present evidence, among the most successful drives conducted by the American Diabetes Association. Over 650 Committees on Diabetes in County and State Medical Societies, in addition to our own 28 Affiliate Associations, were active this year, plus 200 more Medical Societies in which diabetes detection was carried on by the secretaries.

On the educational front, the Week was a real success. The Association's own program familiarized large sectors of the American people with the dangers of diabetes and with methods of discovering the disease. Nearly 425 radio transcriptions were sent out upon request to various Medical Societies for local use, while national programs devoted largely or entirely to Diabetes Week numbered over a dozen. These included a superb 30-minute dramatization of the discovery of insulin; a very informative and amusing interview show put on for the Association by Fred Allen; a dramatization of the Chinese experiences of Mr. and Mrs. Victor Saxl—Mrs. Saxl is a diabetic—called "Tanze Bin"; and several other shorter interview, guest appearance, and spot announcement programs. On television there were about 10 programs that promoted Diabetes Week, including a coast to coast news program that used as one of its daily features during the Week a previously-filmed survey of the National Office, its staff and its operations.

There will be more exhaustive reports on the success of the Week and of the 1951 Diabetes Detection Drive in forthcoming issues of DIABETES. Meanwhile, it is safe to say that 1951's program pointed the way to still more effective and comprehensive undertakings of a similar nature in the future.

WALTER REED SOCIETY

According to an announcement recently received, the National Society for Medical Research last December sponsored the formation of a unique new group to which both lay and professional people may belong. The only qualification for membership in the just-organized Walter Reed Society is that the individual must have served as a subject for some sort of medical experiment. The organizing meeting was held in Los Angeles at the close of the American Medical Association meetings, and Dr. Max Sadove, Head of the Department of Anesthesiology at the University of Illinois, was elected organizing president. Dr. Sadove has frequently served

as a "human guinea pig," the latest experiment in which he participated as "raw material" having to do with artificial respiration. This was performed at the request of the Defense Department.

A. J. Carlson, Ph.D., M.D., the President of the National Society for Medical Research, in announcing the organizing meeting of the Walter Reed Society, stated that dues for members would be $1.00 per year. Scientists who have not only conducted experiments on human subjects but who have also themselves served as experimental material are eligible for designation as Fellows.

PERSONALS

A. L. Chute, M.D., a member of our Association's Council, has been appointed Professor of Pediatrics and Head of the Pediatrics Department at the University of Toronto, and Physician-in-Chief of the Department of Pediatrics at the Hospital for Sick Children.

Although the appointment was made nearly a year ago, those who may not have heard of it at the time will be interested to learn that I. Arthur Mirsky, M.D., is now Professor and Chairman of the Department of Clinical Science at the University of Pittsburgh School of Medicine. He is also at the same time Professor of Research Psychiatry, according to a report in *Science*.

Some misunderstanding may still exist with regard to the nature of the position Russell M. Wilder, M.D., now holds with the U.S. Public Health Service. Dr. Wilder was originally scheduled to be Medical Director of the Clinical Center of the National Institutes of Health at Bethesda, Md. Instead, he more recently accepted the appointment as Director of the National Institute of Arthritis and Metabolic Diseases, also in Bethesda.

MILITARY HOSPITAL DIETS

The manual "Hospital Diets," by the Department of the Army and the Air Force (January 1951—TM 8-500; AM 160-8), devoted Chapter 8, pages 70 to 82, to a "Dietary Program for Diabetics." The diets are taken from the booklet "Meal Planning with Exchange Lists," and due credit is given to the American Diabetes Association, The American Dietetic Association, and the Diabetes Section, U. S. Public Health Service.

CHANGE OF ADDRESS

Mail addressed to the National Office of the American Diabetes Association should hereafter be designated "New York 36"—not "New York 18." The Post Office made this change in the zone number effective as of January 1, 1952.

OBITUARIES

HARRY SAMUEL ARKIN, M.D., died on July 8, 1951, at 58 years of age.

Dr. Arkin was born April 22, 1893. He received his M.D. degree from Rush Medical College in 1917, and engaged in the practice of internal medicine in Chicago. He served for varying terms as Attending Physician at the Michael Reese Hospital and Cook County Hospital, and also at the Winfield Tuberculosis Sanitorium and the Mandel Clinic.

He joined the faculty of the Northwestern Medical School in 1920, and subsequently became Assistant Professor of Medicine. He was a specialist certified by the American Board of Internal Medicine.

Dr. Arkin belonged to the American College of Chest Physicians and the Chicago Tuberculosis Society, as well as to the American Diabetes Association, which he joined in February 1941. He was a Fellow of the American Medical Association.

JACOB M. BLOCK, M.D., a member of the American Diabetes Association since June 1942, died on June 9, 1951, at the age of 51.

Dr. Block graduated from Long Island College Hospital, Brooklyn, N.Y., in 1921, and practiced medicine in Brooklyn all his active life. He served on the staffs of the Wyckoff Heights and Deaconess Bethany Hospitals, and was past president of the Long Island College Alumni.

In addition to being a member of the American Diabetes Association, Dr. Block also belonged to the American Heart Association and the American Congress of Physical Therapy, and was a Fellow of the American Medical Association.

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Subscription rates: 1 year, $2.00; 2 years, $3.50; 3 years, $4.75. Add 25c per year for subscriptions outside the U.S. and Canada.

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